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**Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8)**

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Abstract: Background

Direct comparisons of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors are limited. The SUSTAIN 8 trial compared efficacy and safety of semaglutide versus canagliflozin in patients with T2D.

Methods

In this double-blind, parallel-group trial, adults with uncontrolled T2D (HbA1c 7·0–10·5% [53–91 mmol/mol]) on stable daily metformin were randomly assigned to subcutaneous semaglutide 1·0 mg once weekly or oral canagliflozin 300 mg once daily. Primary and confirmatory secondary endpoints were changes from baseline in HbA1c and body weight, respectively. Primary analysis was based on all randomised patients using on-treatment data collected prior to initiation of rescue medication. The trial was registered with ClinicalTrials.gov (NCT03136484).

Findings

In total, 788 patients were randomised (1:1) at 111 centres; 739 completed the trial. Patients randomised to semaglutide versus canagliflozin had significantly greater reductions in HbA1c and weight (estimated treatment differences [95% confidence intervals]: -0·49%-point [-0·65;-0·33]/ -5·34 mmol/mol [-7·10; -3·57],  $p<0·0001$ , and -1·06 kg [-1·76;-0·36],  $p=0·0029$ , respectively. Gastrointestinal disorders were the most frequent adverse events (AEs) with semaglutide, whereas infections and infestations occurred more frequently with canagliflozin. Premature treatment discontinuation due to AEs occurred in 9·7% and 5·1% of patients randomised to semaglutide and canagliflozin, respectively. One fatal AE confirmed unlikely to be caused by treatment occurred in the semaglutide group.

Interpretation

Once-weekly semaglutide 1·0 mg was superior to daily canagliflozin 300 mg in reducing HbA1c and body weight in patients with T2D uncontrolled on metformin. These outcomes may guide treatment intensification choices.

Funding

Novo Nordisk A/S.

## Title

Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, randomised, controlled trial

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## **RESEARCH IN CONTEXT**

### **Evidence before this study**

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose co-transporter-2 inhibitors (SGLT-2is) are increasingly being used as preferred second-line agents after metformin in the management of type 2 diabetes (T2D) because of additional effects beyond HbA<sub>1c</sub> lowering, including weight loss and improvements in cardiovascular outcomes. However, to date, data on the second-line use of GLP-1RAs versus SGLT-2is are limited, making it difficult for physicians to make informed decisions on treatment choices for patients with T2D inadequately controlled with metformin alone.

### **Added value of this study**

The results of the SUSTAIN 8 trial demonstrated that subcutaneous semaglutide 1·0 mg once weekly was superior to oral canagliflozin 300 mg daily in reducing HbA<sub>1c</sub> and body weight in adults with T2D inadequately controlled with daily metformin. The safety profile of semaglutide 1·0 mg was generally similar to that of canagliflozin, and higher rates of certain adverse events (AEs) with each treatment were as expected (gastrointestinal AEs with semaglutide, and genital and perineal infections with canagliflozin). Rates of hypoglycaemia were low with both treatments.

### **Implications of the available evidence**

SUSTAIN 8 provides direct evidence of the superiority of semaglutide 1·0 mg over canagliflozin 300 mg in reducing HbA<sub>1c</sub> and body weight, as well as demonstrating similar safety profiles. These findings support the use of semaglutide as an alternative to canagliflozin in second-line treatment of patients with T2D who need treatment intensification after metformin.

## **ABSTRACT**

### **Background**

Direct comparisons of glucagon-like peptide-1 receptor agonists and sodium–glucose cotransporter-2 inhibitors are limited. The SUSTAIN 8 trial compared efficacy and safety of semaglutide versus canagliflozin in patients with T2D.

### **Methods**

In this double-blind, parallel-group trial, adults with uncontrolled T2D (HbA<sub>1c</sub> 7·0–10·5% [53–91 mmol/mol]) on stable daily metformin were randomly assigned to subcutaneous semaglutide 1·0 mg once weekly or oral canagliflozin 300 mg once daily. Primary and confirmatory secondary endpoints were changes from baseline in HbA<sub>1c</sub> and body weight, respectively. Primary analysis was based on all randomised patients using on-treatment data collected prior to initiation of rescue medication. The trial was registered with ClinicalTrials.gov (NCT03136484).

### **Findings**

In total, 788 patients were randomised (1:1) at 111 centres; 739 completed the trial. Patients randomised to semaglutide versus canagliflozin had significantly greater reductions in HbA<sub>1c</sub> and weight (estimated treatment differences [95% confidence intervals]: –0·49%-point [–0·65;–0·33]/ –5·34 mmol/mol [–7·10; –3·57],  $p<0\cdot0001$ , and –1·06 kg [–1·76;–0·36],  $p=0\cdot0029$ , respectively. Gastrointestinal disorders were the most frequent adverse events (AEs) with semaglutide, whereas infections and infestations occurred more frequently with canagliflozin. Premature treatment discontinuation due to AEs occurred in 9·7% and 5·1% of patients randomised to semaglutide and canagliflozin, respectively. One fatal AE confirmed unlikely to be caused by treatment occurred in the semaglutide group.

### **Interpretation**

Once-weekly semaglutide 1·0 mg was superior to daily canagliflozin 300 mg in reducing HbA<sub>1c</sub> and body weight in patients with T2D uncontrolled on metformin. These outcomes may guide treatment intensification choices.

**Funding** Novo Nordisk A/S



## INTRODUCTION

Current guidelines for the comprehensive management of type 2 diabetes (T2D) recommend a patient-centred approach to guide the choice of pharmacologic agents.<sup>1–3</sup> Beyond optimising glycaemic control, other treatment considerations include impact on weight, hypoglycaemia risk, and comorbidities.<sup>2</sup> Both glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter-2 inhibitors (SGLT-2is) are preferred add-on treatment options for patients with cardiovascular disease (CVD) and poorly controlled HbA<sub>1c</sub> after first-line metformin and lifestyle modifications.<sup>1–3</sup>

Semaglutide is a GLP-1RA with proven efficacy across the continuum of diabetes care, as demonstrated in the SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) clinical trial programme, in which subcutaneous once-weekly semaglutide demonstrated superior HbA<sub>1c</sub> and body weight reductions versus placebo, sitagliptin, exenatide extended release, insulin glargine, and dulaglutide.<sup>4–9</sup> Canagliflozin, a once-daily oral SGLT-2i, also has proven efficacy in glycaemic control and weight loss versus placebo and active comparators.<sup>10–13</sup> Both semaglutide and canagliflozin provide cardiovascular (CV) benefits in patients with T2D at high risk of CVD.<sup>14,15</sup>

Although GLP-1RAs and SGLT-2is are increasingly used as second-line agents, diabetes guidelines make few recommendations for the choice of one class over another. With many available treatment options but little robust data to support an evidence-based choice, an individualised approach to patient care can be difficult. We therefore undertook the SUSTAIN 8 study to compare the effect of semaglutide 1·0 mg with canagliflozin 300 mg on reductions in HbA<sub>1c</sub> and body weight in individuals with uncontrolled T2D.

## METHODS

### *Trial design and participants*

SUSTAIN 8 was a 52-week, phase 3b, randomised, double-blind, double-dummy, active-comparator, two-arm, parallel-group trial. Patients were screened by investigators at 115 sites, and the trial was conducted at 111 centres in 11 countries. Trial design and list of investigators are provided in the appendix.

Adults (age  $\geq 18$  years) with T2D were eligible if HbA<sub>1c</sub> levels were 7.0–10.5% (53–91 mmol/mol) on a stable daily dose of metformin ( $\geq 1500$  mg or maximum tolerated dose) for  $\geq 90$  days prior to screening and estimated glomerular filtration rate (eGFR) of  $\geq 60$  mL/min/1.73 m<sup>2</sup>. Key exclusion criteria included history or presence of pancreatitis (acute/chronic), history of diabetic ketoacidosis, myocardial infarction, stroke, hospitalisation for unstable angina, or transient ischaemic attack  $\leq 180$  days prior to screening, and Class IV heart failure. A full list of inclusion/exclusion criteria is provided in the appendix. Metformin was the only background diabetes medication allowed; patients continued the pre-trial dose throughout the treatment period unless rescue medication was required. The trial was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent. This trial is registered with ClinicalTrials.gov, NCT03136484. The protocol and statistical analysis plan are available in the appendix.

#### *Randomisation and masking*

Eligible patients were randomly assigned 1:1 to receive semaglutide 1.0 mg once weekly or canagliflozin 300 mg once daily via an interactive web response system (IWRS). Randomisation was stratified according to participation in a body composition substudy (results reported separately), and allocation of trial products were accomplished using the IWRS. Patients and investigators remained masked throughout the trial; unblinding occurred only when required for medical emergencies. To fulfill masking of the trial, a double-dummy design was implemented, in which all patients randomly assigned to semaglutide also received canagliflozin placebo tablets, while patients randomly assigned to canagliflozin also received semaglutide placebo injections.

#### *Procedures*

A screening period of 2 weeks was followed by 52 weeks of treatment and a 5-week follow-up. The maintenance dose of semaglutide 1.0 mg was reached after an 8-week fixed dose-escalation period. Semaglutide was administered once weekly subcutaneously in the thigh, abdomen or upper arm at any time of day, irrespective of meals, on the same day of the week. Canagliflozin was administered once daily as oral tablets, preferably taken before the first meal of the day, and followed an 8-week fixed-dose escalation.

In patients whose eGFR fell persistently to below 60 mL/min/1.73 m<sup>2</sup>, the dose of canagliflozin or canagliflozin placebo was reduced to 100 mg once daily and re-escalated if eGFR increased to  $\geq 60$  mL/min/1.73 m<sup>2</sup>. All investigational treatments were discontinued if eGFR was reduced to <45 mL/min/1.73 m<sup>2</sup>.

Rescue medication was offered to patients with confirmed fasting plasma glucose levels >13.3 mmol/L (240 mg/dL) from week 8 to the end of week 13, >11.1 mmol/L (200 mg/dL) from week 14 to end of treatment, or HbA<sub>1c</sub> >8.5% (69 mmol/mol) from week 26 to end of treatment. Choice of rescue medication was at the investigator's discretion and excluded GLP-1RAs, dipeptidyl peptidase-4 inhibitors, amylin analogues, and SGLT-2is.

### *Outcomes*

Primary and confirmatory secondary endpoints were changes in HbA<sub>1c</sub> (%-point) and body weight (kg), respectively, from baseline to week 52. Prespecified supportive secondary efficacy endpoints included: achievement of target HbA<sub>1c</sub> levels established by the American Diabetes Association (ADA) (<7.0%; <53 mmol/mol)<sup>16</sup> and the American Association of Clinical Endocrinologists (AACE) ( $\leq 6.5\%$ ;  $\leq 48$  mmol/mol)<sup>1</sup>; weight-loss responses of  $\geq 3\%$ ,  $\geq 5\%$ ,  $\geq 10\%$ ; composite endpoint of HbA<sub>1c</sub> <7.0% (<53 mmol/mol), no weight gain, and no severe hypoglycaemia (ADA<sup>16</sup> classification) or blood glucose-confirmed symptomatic hypoglycaemic episodes; and composite endpoint of HbA<sub>1c</sub> reduction of  $\geq 1\%$ -point and weight loss  $\geq 5\%$ . A *post hoc* analysis also assessed weight-loss responses  $\geq 15\%$ .

Other prespecified secondary efficacy endpoints were change from baseline to week 52 in fasting plasma glucose, 7-point self-measured blood glucose profile, systolic and diastolic blood pressure, fasting blood lipids (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C] and triglycerides), and patient-reported outcomes as assessed by the Diabetes Treatment Satisfaction Questionnaire (DTSQs), Control of Eating Questionnaire (CoEQ), and Short-Form health survey (SF-36v2™).

Supportive safety endpoints included treatment-emergent adverse events (AEs) and severe or blood glucose-confirmed symptomatic hypoglycaemic episodes.

Procedures and assessments for primary and secondary outcome measures are summarised in the appendix.

### *Statistical analysis*

The primary estimand was defined as the treatment difference between semaglutide and canagliflozin at week 52 for all randomised patients if all patients completed treatment and did not start rescue medication. A sample size of 784 ensured a power of >90% for confirming HbA<sub>1c</sub> superiority and body weight superiority with semaglutide versus canagliflozin under reasonable assumptions (efficacy: HbA<sub>1c</sub> -0.32%, body weight -2.4 kg; in-trial treatment effect: HbA<sub>1c</sub> -0.26%, body weight -2.0 kg; standard deviation: HbA<sub>1c</sub> 1.1%, body weight 4.0 kg). A closed testing procedure was used to control the overall type-1 error at a nominal two-sided 5% level (appendix).

Analysis sets included the full analysis set (FAS) of all patients randomly assigned to treatment and the safety analysis set of all patients exposed to  $\geq 1$  dose of trial product. The primary estimand was based on the FAS using post-baseline measurements up to and including week 52 from the 'on-treatment without rescue medication' observation period, an analysis of covariance with treatment, stratification, region, and baseline value as fixed effects, and multiple imputation for missing data. Missing values were imputed using observed data within the same treatment arm using a regression model including region and stratification factor as categorical effects and data from baseline and all previous visits as covariates.

Sensitivity analyses were performed to confirm robustness of conclusions from the primary analysis and included: a tipping-point analysis (pattern-mixture model) based on the FAS using the 'on-treatment without rescue medication' observation period; retrieved dropout analysis based on the FAS using post-baseline measurements up to and including week 52 from the in-trial observation period; and multiple imputation for missing data, in which missing values were imputed using observed data within the same group as defined for the specific analysis (appendix).

### *Role of the funding source*

The sponsor, Novo Nordisk, designed the study and undertook site monitoring, data collection, data analysis and data interpretation. Site investigators gathered data. The first author had full access to all data and had final responsibility for the decision to submit for publication. The sponsor funded editorial support, provided by a professional medical writer.

## RESULTS

The study began on March 15, 2017 and ended on November 16, 2018. In total, 1212 patients were screened, 788 patients were enrolled and randomly assigned to semaglutide 1·0 mg or canagliflozin 300 mg (FAS; n=394 in each treatment arm), and 786 (99·7%) were exposed to treatment (figure 1). Two patients were randomly assigned to semaglutide but not exposed (reasons unknown).

Of the FAS, 673 (85·4%) patients completed treatment (semaglutide, n=330; canagliflozin, n=343), and 739 (93·8%) completed the trial (semaglutide, n=367; canagliflozin, n=372). Overall, 29 patients (7·4%) in the semaglutide group and 27 patients (6·6%) in the canagliflozin group received rescue medication. The majority of patients initiating rescue medication had baseline HbA<sub>1c</sub> >8·5% (>69 mmol/mol). The most commonly used rescue medication was sulphonylurea (semaglutide, n=25/29 [86·2%]; canagliflozin, n=19/27 [70·4%]). Baseline characteristics were similar across treatment groups, including the number of patients with complications from diabetes at screening (table 1).

### *Efficacy*

For both treatment arms, mean baseline (standard deviation [SD]) HbA<sub>1c</sub> decreased over time from a pooled baseline average of 8·3% (1·0) (66·7 mmol/mol [11·1]; figure 2A). Treatment with semaglutide led to superior reductions in HbA<sub>1c</sub> compared with canagliflozin, with an estimated change (standard error [SE]) from baseline to week 52 of –1·5%-point (0·06) (–16·0 mmol/mol [0·65]) with semaglutide and –1·0%-point (0·06) (–10·7 mmol/mol [0·61]) with canagliflozin. The estimated treatment difference (ETD) [95% confidence interval (CI)] was –0·49%-point [–0·65;–0·33] (–5·34 mmol/mol [–7·10;–3·57]); p<0·0001. Greater proportions of patients achieved prespecified HbA<sub>1c</sub> targets with semaglutide versus canagliflozin (<7·0% [<53 mmol/mol]: 66·1% vs 45·1%; odds ratio [OR] [95% CI] 2·77 [1·98;3·85], p<0·0001; ≤6·5% [≤48 mmol/mol]: 52·8% vs 23·6%; OR [95% CI] 4·19 [2·97;5·92], p<0·0001, respectively) (appendix).

Semaglutide also demonstrated superior reductions in body weight from baseline to week 52 (figure 2B). From an overall mean baseline (SD) of 90·2 kg (22·6), estimated change (SE) in body weight was –5·3 kg (0·26) with semaglutide and –4·2 kg (0·24) with canagliflozin (ETD [95% CI] –1·06 kg [–1·76;–0·36]; p=0·0029). Greater proportions of patients achieved weight loss of ≥3%, ≥5% and ≥10% with semaglutide versus canagliflozin,

although the difference was only significant in patients achieving  $\geq 10\%$  weight loss (22.3% vs 8.9%; OR [95% CI] 2.99 [1.89;4.75];  $p < 0.0001$ ). A *post hoc* analysis demonstrated weight loss  $\geq 15\%$  was achieved by a greater proportion of semaglutide- than canagliflozin-treated patients (6.8% vs 0.9%, respectively; OR [95% CI] 7.45 [2.45;22.6];  $p = 0.0004$ ; appendix).

In addition, more patients in the semaglutide versus canagliflozin group achieved composite endpoints of HbA<sub>1c</sub>  $< 7.0\%$  ( $< 53$  mmol/mol), no weight gain and no severe or blood glucose-confirmed hypoglycaemia (59.9% vs 39.9%; OR [95% CI] 2.56 [1.84;3.54];  $p < 0.0001$ ) and HbA<sub>1c</sub> reduction  $\geq 1.0\%$ -point ( $\geq 10.4$  mmol/mol) and weight loss  $\geq 5\%$  (39.2% vs 24.3%; OR [95% CI] 1.99 [1.43;2.76];  $p < 0.0001$ ).

Reductions in mean fasting plasma glucose and self-measured blood glucose (mean 7-point profile and mean postprandial increments) from baseline to week 52 were all greater with semaglutide than canagliflozin ( $p = 0.0094$ ,  $p < 0.0001$ , and  $p = 0.036$ , respectively; table 2). Both treatments resulted in reductions in blood pressure and fasting lipids. Canagliflozin reduced systolic and diastolic blood pressure versus semaglutide from baseline to week 52 (ETD [95% CI] 2.0 mmHg [0.0;4.0],  $p = 0.045$ ; and 2.0 mmHg [0.7;3.4],  $p = 0.003$ , respectively) (table 2). Pulse rate increased by a mean (SE) 2.7 (0.4) bpm with semaglutide, compared with a mean reduction of 0.6 (0.4) bpm with canagliflozin (ETD [95% CI] 3.3 [2.1;4.5];  $p < 0.0001$ ). Semaglutide reduced total serum cholesterol, LDL-C and triglycerides versus canagliflozin from baseline to week 52 (total and LDL-C,  $p < 0.001$ ; triglycerides,  $p = 0.040$ ) (table 2; appendix). Canagliflozin increased HDL-C versus semaglutide from baseline to week 52 ( $p = 0.0001$ ) (table 2).

#### *Patient-reported outcomes*

There was no difference in DTSQ score (overall and individual components) between semaglutide and canagliflozin, except for in ‘satisfaction with current treatment’, where the score was in favour of semaglutide (ETD [95% CI] 0.13 [0.00;0.26];  $p < 0.05$ ) (appendix).

For the CoEQ, there was no difference between semaglutide and canagliflozin in any domain, with the exception of the savoury craving domain score, where the score was in favour of semaglutide (ETD [95% CI] -0.28 [-0.54;-0.03];  $p = 0.030$ ; appendix).

Results of the SF-36v2 questionnaire demonstrated no differences between treatment arms for changes in overall health-related quality of life (data not shown).

### *Safety*

In total, 1189 AEs were reported by 76.0% (298/392) of patients in the semaglutide group, and 1138 AEs were reported by 71.8% (283/394) of patients in the canagliflozin group (table 3). Most AEs were mild (semaglutide: 66.8% [262/392]; canagliflozin: 64.0% [252/394]) or moderate (semaglutide: 35.5% [139/392]; canagliflozin: 29.9% [118/394]) in severity. Thirty serious AEs were reported by 4.6% (18/392) of semaglutide-treated patients, and 35 serious AEs were reported by 5.3% (21/394) of canagliflozin-treated patients (table 3).

The most frequent AEs with semaglutide were gastrointestinal disorders (184/392 [46.9%] vs 110/394 [27.9%] with canagliflozin), whereas infections and infestations were the most frequent AEs with canagliflozin (136/394 [34.5%] vs 114/392 [29.1%] with semaglutide). A higher proportion of patients in the semaglutide group prematurely discontinued treatment due to an AE versus the canagliflozin group (38/392 [9.7%] vs 20/394 [5.1%]). This was primarily driven by gastrointestinal AEs in the semaglutide group (26/392 [6.6%] vs 4/394 [1.0%] for canagliflozin). The most common reason for premature treatment discontinuation in the canagliflozin group was infections and infestations (6/394 [1.5%] vs 1/392 [0.3%] for semaglutide). Severe or blood glucose-confirmed symptomatic hypoglycaemia occurred in six (1.5%) and five (1.3%) patients in the semaglutide and canagliflozin groups, respectively. Two events in one patient (0.3%) from the semaglutide group were considered severe; both resolved after treatment with oral carbohydrates. Retinopathy occurred in 9/392 [2.3%] patients with semaglutide versus 15/394 [3.8%] with canagliflozin.

No amputations occurred in the trial. One fatal adverse event (0.3%) that did not meet the criteria for a coronary event occurred in the semaglutide group and was confirmed by the Event Adjudication Committee as sudden cardiac death unlikely to be caused by the treatment. No clinically relevant changes in other safety parameters were observed.

## DISCUSSION

SUSTAIN 8 demonstrates the superiority of once-weekly semaglutide 1·0 mg versus daily canagliflozin 300 mg on reductions in HbA<sub>1c</sub> and body weight in patients with uncontrolled T2D on a background of metformin, although both treatments led to improvements in glycaemia and weight. These results add to those observed in the SUSTAIN clinical trial programme, in which treatment with semaglutide led to superior improvements in glycaemic control and weight loss versus placebo, sitagliptin, exenatide extended release, insulin glargine and dulaglutide.<sup>4–9</sup>

Achieving HbA<sub>1c</sub> targets <7·0% (<53 mmol/mol)<sup>16</sup> or ≤6·5% (≤48 mmol/mol)<sup>1</sup> is critical in substantially reducing the development and progression of microvascular complications in T2D.<sup>16</sup> Both semaglutide<sup>4–9</sup> and canagliflozin<sup>10–13</sup> have previously demonstrated efficacy in reducing HbA<sub>1c</sub> to target levels. In SUSTAIN 8, the 1·5%-point (16·0 mmol/mol) reduction in HbA<sub>1c</sub> with semaglutide is consistent with reported mean reductions of 1·5–1·8% points in previous trials.<sup>17</sup> Similarly, the 1·0%-point (10·7 mmol/mol) reduction in HbA<sub>1c</sub> achieved with canagliflozin is consistent with the 0·80–1·03%-point reduction reported in the literature.<sup>18,19</sup> Approximately two-thirds of patients taking semaglutide achieved the ADA target of <7·0% (<53 mmol/mol), and over half met the more ambitious AACE target of ≤6·5% (≤48 mmol/mol), compared with less than half and less than a quarter, respectively, of those taking canagliflozin. These results are similar to those from responder analyses of the global SUSTAIN clinical trial programme for semaglutide<sup>20</sup> and phase 3 studies with canagliflozin<sup>10,11</sup> and reflect those of a network meta-analysis evaluating the comparative efficacy of semaglutide and canagliflozin in patients with T2D inadequately controlled with metformin.<sup>21</sup>

In SUSTAIN 8, twice as many patients achieved weight loss ≥10% with semaglutide compared with canagliflozin after 1 year of treatment, with 6·8% of patients treated with semaglutide patients as ‘super-responders’ achieving a 15% weight loss, as demonstrated via a pre-defined supportive secondary endpoint and in a *post hoc* analysis. These results are similar to the greater proportions of weight-loss responders with semaglutide versus comparators observed in SUSTAIN 1–5 and 7.<sup>22</sup> Factors contributing to the magnitude of weight loss observed with semaglutide are not fully understood. In SUSTAIN 9, the addition of semaglutide to an SGLT-2i significantly reduced body weight versus placebo (ETD [95% CI] –3·81 kg [–4·70;–2·93]),<sup>23</sup> an additive effect that suggests a difference in mechanism of action for weight loss between drug classes and a possible synergy when used concomitantly. The effect of GLP-1RAs on weight loss is believed to be centrally mediated,<sup>24</sup> with reduced energy intake as a potential



result of reduced appetite and food cravings, better control of eating, and a lower preference for fatty food.<sup>25</sup> SGLT-2is are generally considered to cause weight loss via glucose excretion (calorie loss) in the kidneys, although this glycosuria can elicit adaptive compensatory increases in energy intake to mitigate excessive weight loss.<sup>26</sup>

Surprisingly, patient-reported outcomes in SUSTAIN 8 demonstrate improved control of cravings with both agents, although semaglutide significantly decreased the desire for savoury food compared with canagliflozin (appendix).

In SUSTAIN 8, semaglutide reduced levels of total cholesterol, LDL-C, and triglycerides, results that have been observed in previous trials<sup>4,6-9,14,23</sup> Hyperlipidaemia is a well-known risk factor for CVD and a particular concern for patients with T2D.<sup>27</sup> The beneficial effects of semaglutide on lipids may have played a role in the CV risk reduction demonstrated in SUSTAIN 6, in which treatment with semaglutide significantly decreased the occurrence of major CV events versus placebo in patients at high risk of CVD.<sup>14</sup>

The results of SUSTAIN 8 demonstrate low rates of serious AEs for both semaglutide and canagliflozin. The reported higher incidence of GI AEs with semaglutide was expected, with rates similar to those across the SUSTAIN programme.<sup>4-9</sup> Likewise, the higher incidence of genital and perineal infections with canagliflozin was expected and reported previously.<sup>10-13</sup> Severe or blood-glucose confirmed hypoglycaemia was low and similar in both treatment arms. These results, combined with consistently low rates of hypoglycaemic events reported across the SUSTAIN trials,<sup>4-9</sup> may offer further reassurance to patients with T2D for whom fear of hypoglycaemia may be a barrier to achieving glycaemic control.

The superiority of semaglutide on HbA<sub>1c</sub> and weight loss versus canagliflozin is consistent with indirect evidence from clinical trials investigating the efficacy of GLP-1RAs versus SGLT-2is. In a network meta-analysis that indirectly compared the efficacy of semaglutide and SGLT-2is (including canagliflozin and dapagliflozin) in patients with T2D inadequately controlled with metformin, semaglutide outperformed SGLT-2i comparators for both glycaemic control and weight loss.<sup>21</sup> Similarly, another network meta-analysis demonstrated superiority of GLP-1RAs versus SGLT-2is.<sup>28</sup> Recently, the PIONEER-2 trial demonstrated significantly greater effects of once-daily oral semaglutide on glycaemic control and weight loss compared with empagliflozin at 52 weeks.<sup>29</sup>

Overall, results of SUSTAIN 8 provide a robust head-to-head comparison of a GLP-1RA and SGLT-2i and confirm that semaglutide is an efficacious, well-tolerated second-line treatment option for patients with T2D.

Strengths of SUSTAIN 8 include its substantial size, global population, double-blind nature, relatively long treatment period, and relevant head-to-head comparison with a well-established glucose-lowering medication. However, as with any randomised, controlled trial with multiple eligibility criteria, the population of SUSTAIN 8 may not accurately reflect the real-world, heterogeneous T2D population.

In summary, treatment with once-weekly semaglutide 1·0 mg was superior to daily canagliflozin 300 mg in reducing HbA<sub>1c</sub> and body weight in patients with uncontrolled T2D on a background of metformin. Both treatments were well tolerated, with low rates of hypoglycaemia. These results add to a body of evidence confirming semaglutide as an effective glucose-lowering medication offering additional benefits of weight loss, reduced risk of hypoglycaemia, and CV-protective effects. These study outcomes may be used to guide decisions about treatment intensification following metformin therapy in this patient population.

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### *Author contributions*

I.L., A-M.C., H.K., C.W.I.R., D.T., A.V., and R.M. participated in the design of this analysis. I.L., A-M.C., J.P.F., H.K., C.W.I.R., D.T., A.V., and R.M. contributed to the conduct and data collection of the primary trial. N.L.L. contributed to the data analysis. All authors interpreted the data and participated in writing the report, with the support of medical writing services provided by the funder. All authors read and approved the submitted version of the report.

### *Information on author access to data*

The first author (I.L.) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

### *Declaration of interests*

I.L. received research grants to her institution and consulting fees from Novo Nordisk during the conduct of the study. Outside the submitted work, she has received grants and/or personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GI Dynamics, Intarcia, Mannkind, Merck, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi, TARGET PharmaSolutions, and Valeritas.

A-M.C., N.L.L., and D.T. are full-time employees of Novo Nordisk A/S.

J.P.F. reports grants and personal fees from Novo Nordisk during the conduct of the study and grants and personal fees from AstraZeneca Eli Lilly, Pfizer, and Sanofi outside the submitted work.

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R.M. reports personal fees from Eli Lilly, Novo Nordisk, and Sanofi outside the submitted work.

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This study was supported by Novo Nordisk A/S, Denmark. The funding sources contributed to the design and conduct of the trial, the analysis and interpretation of the data, review and approval of the manuscript.

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#### *Data sharing*

<b>Will individual participant data be available (including data dictionaries)?</b>	Individual participant data will be shared in data sets in a de-identified/anonymised format.
<b>What data in particular will be shared?</b>	Data sets from Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the EU and US.
<b>What other documents will be available?</b>	The study protocol and redacted Clinical Study Report (CSR) will be available according to Novo Nordisk data sharing commitments.
<b>When will data be available (start and end dates)?</b>	The data will be available permanently after research completion and approval of product and product use in both EU and US. No end date.

<b>With whom will data be shared?</b>	With bona fide researchers submitting a research proposal and requesting access to data.
<b>For what types of analyses?</b>	For use as approved by the Independent Review Board (IRB) according to the IRB Charter (see <a href="http://www.novonordisk-trials.com">www.novonordisk-trials.com</a> ).
<b>By what mechanism will data be made available?</b>	The access request proposal form and the access criteria can be found at <a href="http://www.novonordisk-trials.com">www.novonordisk-trials.com</a> . The data will be made available on a specialised SAS data platform.

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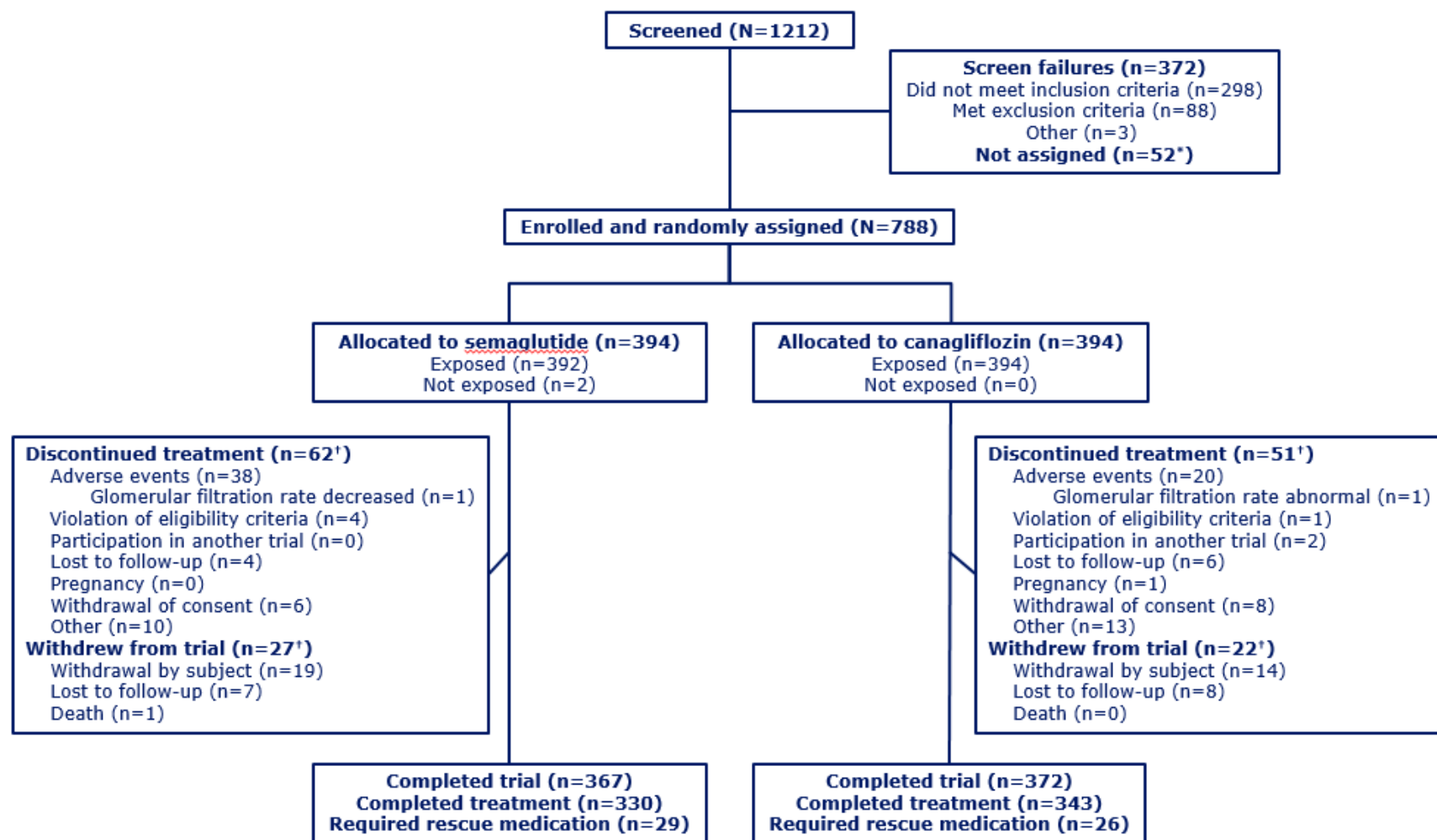
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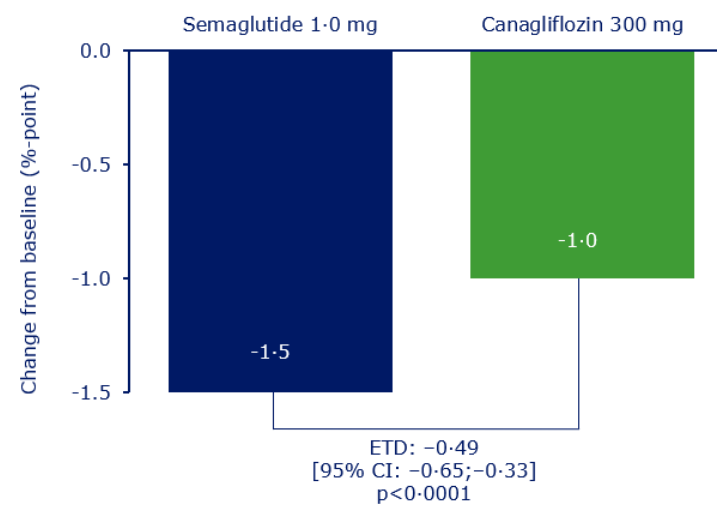
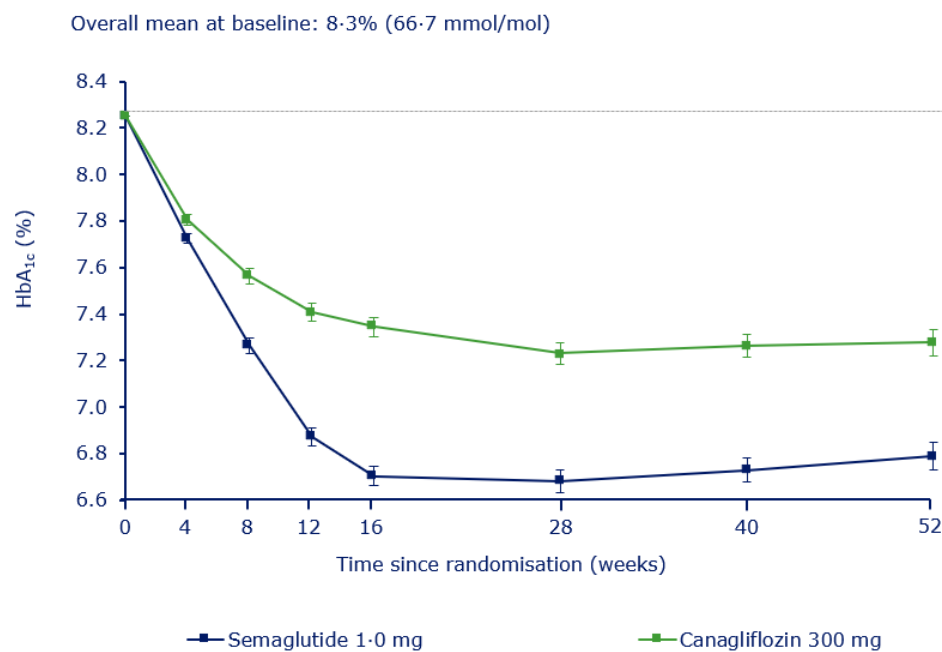
**Figure 1: SUSTAIN 8 patient disposition**



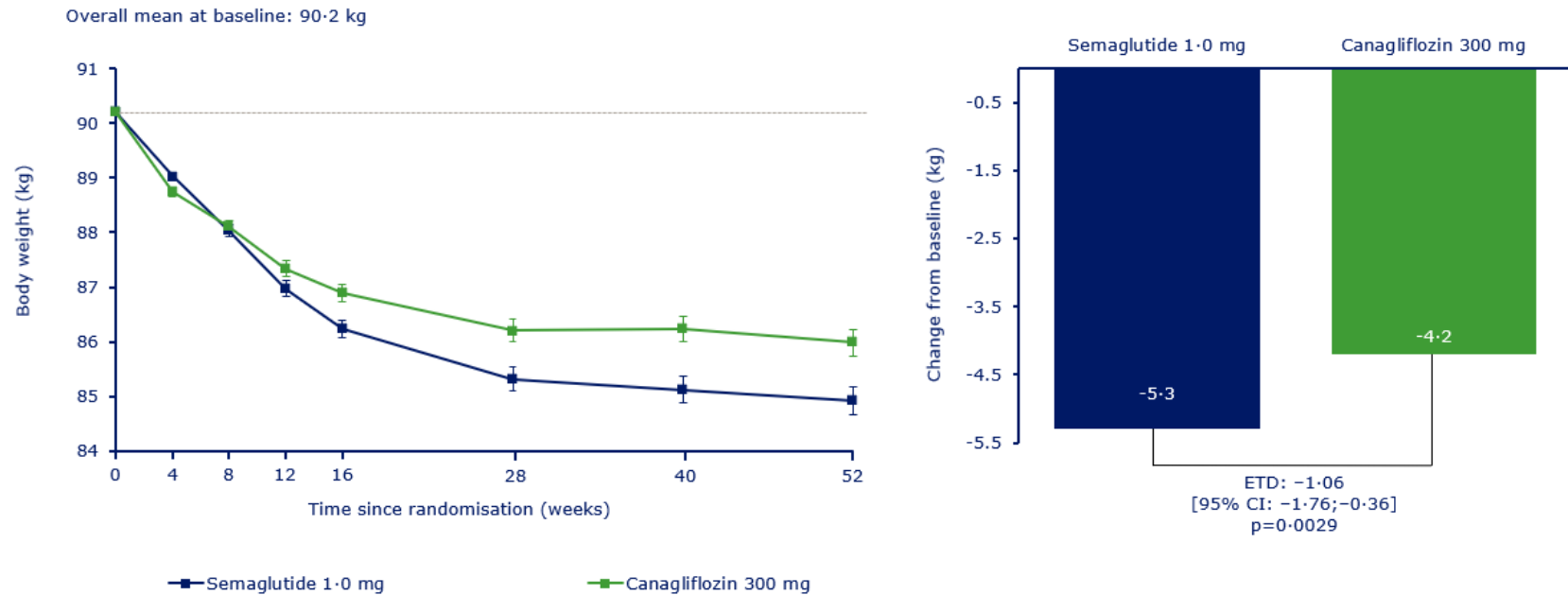
\*Not assigned includes patients who withdrew consent before randomisation. †Patients who discontinued treatment and who withdrew from the study were partially overlapping.

**Figure 2: Glycaemic and body weight outcomes**

A. Estimated mean HbA<sub>1c</sub> by week and change from baseline at week 52



B. Estimated mean body weight by week and change from baseline at week 52



‘On treatment without rescue medication’ data for all patients randomly assigned to treatment. A. Change in HbA<sub>1c</sub> by week and from overall baseline at week 52. Mean estimates are from an ANCOVA with treatment, region and stratification factor as fixed factors and baseline value as covariate where missing data were multiple imputed using data from patients within the same group defined by randomised treatment using a regression model including region and stratification factor as categorical effects and data from baseline and all previous visits as covariates. B. Estimated mean body weight by week and change from baseline. Change in body weight over time and from overall baseline at week 52. For A and B, error bars are  $\pm 1$  standard error of the means and dashed lines indicate the overall mean values at baseline. All site visits, except screening visits, were to be completed in fasting state. ANCOVA=analysis of covariance. CI=confidence interval. ETD=estimated treatment difference.

**Table 1: Baseline characteristics**

	<b>Semaglutide 1·0 mg (n=394)</b>	<b>Canagliflozin 300 mg (n=394)</b>	<b>Total (N=788)</b>
Age, years	55·7 (11·1)	57·5 (10·7)	56·6 (10·9)
Male sex, n (%)	223 (56·6)	201 (51·0)	424 (53·8)
Ethnicity, n (%)			
Hispanic or Latino	156 (39·6)	137 (34·8)	293 (37·2)
Not Hispanic or Latino	238 (60·4)	257 (65·2)	495 (62·8)
Race, n (%)			
American Indian or Alaska native	1 (0·3)	3 (0·8)	4 (0·5)
Asian	62 (15·7)	63 (16·0)	125 (15·9)
Black or African American	28 (7·1)	30 (7·6)	58 (7·4)
White	297 (75·4)	290 (73·6)	587 (74·5)
Other	6 (1·5)	7 (1·8)	13 (1·6)
Not applicable	0	1 (0·3)	1 (0·1)
HbA <sub>1c</sub> , %	8·3 (1·0)	8·2 (1·0)	8·3 (1·0)
HbA <sub>1c</sub> , mmol/mol	67·1 (11·1)	66·3 (10·6)	66·7 (10·9)
Glucose, mmol/L			
FPG	9·4 (2·7)	9·4 (2·6)	9·4 (2·7)
Mean 7-point SMBG	10·3 (2·4)	10·6 (2·6)	10·4 (2·5)
Postprandial SMBG increments	2·1 (1·9)	2·2 (1·8)	2·2 (1·8)
Diabetes duration, years	7·5 (5·9)	7·2 (5·4)	7·4 (5·6)

Body weight, kg	90.6 (22.6)	89.8 (22.6)	90.2 (22.6)
BMI, kg/m <sup>2</sup>	32.2 (6.8)	32.5 (6.9)	32.3 (6.8)
Systolic blood pressure, mmHg	129.4 (14.7)	131.4 (14.8)	130.4 (14.8)
Diastolic blood pressure, mmHg	78.9 (9.3)	79.5 (9.0)	79.2 (9.2)
Lipids, mmol/L*			
Total cholesterol	4.5 (22.6)	4.4 (24.9)	4.4 (23.7)
HDL-C	1.1 (24.6)	1.1 (23.9)	1.1 (24.3)
LDL-C	2.4 (37.6)	2.4 (42.3)	2.4 (40.0)
Triglycerides	1.8 (53.3)	1.8 (51.5)	1.8 (52.4)
Renal function (eGFR), <sup>†</sup> n (%)			
Normal	285 (72.3)	275 (69.8)	560 (71.1)
Mild renal impairment	107 (27.2)	117 (29.7)	224 (28.4)
Moderate renal impairment	2 (0.5)	2 (0.5)	4 (0.5)
Severe renal impairment or end-stage renal disease	0	0	0
Diabetic complications, n (%)			
Diabetic neuropathy	44 (11.2)	45 (11.4)	89 (11.3)
Diabetic retinopathy	33 (8.4)	32 (8.1)	65 (8.2)
Macroangiopathy	19 (4.8)	19 (4.8)	38 (4.8)
Diabetic nephropathy	11 (2.8)	17 (4.3)	28 (3.6)
Macular oedema	2 (0.5)	2 (0.5)	4 (0.5)
Antidiabetes medication at screening, n (%)			
Biguanides	394 (100)	394 (100)	788 (100)
Insulin and analogues for injection <sup>‡</sup>	1 (0.3)	0 (0)	1 (0.1)

Values are mean (SD) or n (%) for the full analysis set, unless otherwise stated. \*Geometric mean (coefficient of variation). <sup>†</sup>Renal function was defined as normal: eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>; mild renal impairment: eGFR  $\geq 60$  to  $<90$  mL/min/1.73 m<sup>2</sup>; moderate renal impairment: eGFR  $\geq 30$  to  $<60$  mL/min/1.73 m<sup>2</sup>; severe renal impairment: eGFR  $\geq 15$  to  $<30$  mL/min/1.73 m<sup>2</sup>; end-stage renal disease: eGFR  $<15$  mL/min/1.73 m<sup>2</sup>. <sup>‡</sup>Patients randomly assigned in error. BMI=body mass index. eGFR=estimated glomerular filtration rate. FPG=fasting plasma glucose. HDL-C=high-density lipoprotein cholesterol. LDL-C=low-density lipoprotein cholesterol. SMBG=self-measured blood glucose.

**Table 2: Glucose, blood pressure, and lipids at 52 weeks**

	<b>Semaglutide 1·0 mg (n=394)</b>	<b>Canagliflozin 300 mg (n=394)</b>		
<b>Change from baseline</b>			<b>ETD [95% CI]</b>	<b>p-value</b>
Glucose, mmol/mol				
FPG	−2·32 (0·10)	−1·97 (0·10)	−0·36 [−0·63;−0·09]	0·0094
Mean 7-point SMBG profile	−2·8 (0·10)	−2·0 (0·10)	−0·86 [−1·14;−0·58]	<0·0001
Postprandial SMBG increments	−0·7 (0·09)	−0·4 (0·09)	−0·26 [−0·49;−0·02]	0·036
Systolic blood pressure, mmHg	−3·5 (0·7)	−5·5 (0·7)	2 [0;4·0]	0·045
Diastolic blood pressure, mmHg	−1·0 (0·5)	−3·0 (0·5)	2 [0·7;3·4]	0·003
<b>Ratio to baseline</b>			<b>ETR [95% CI]</b>	<b>p-value</b>
Lipids, mmol/L				
Total cholesterol	0·97 (0·01)	1·03 (0·01)	0·94 [0·92;0·97]	<0·0001
LDL-C	0·97 (0·02)	1·05 (0·02)	0·92 [0·88;0·96]	0·0004
HDL-C	1·04 (0·01)	1·08 (0·01)	0·96 [0·94;0·98]	0·0001
Triglycerides	0·87 (0·02)	0·92 (0·02)	0·95 [0·90;1·00]	0·040

‘On-treatment without rescue medication’ data. Values are mean (SE). Responses were analysed using an ANCOVA with treatment, region and stratification factor as fixed factors and baseline value as covariate. Before analysis, missing data were multiple imputed using observed data from patients within the same group defined by randomised treatment, using a regression model including region and stratification factor as categorical effects and data from baseline and all previous visits as covariates. For lipids, the response and baseline value were log transformed prior to analysis. CI=confidence interval. ETD=estimated treatment

difference. ETR=estimated treatment ratio. FPG=fasting plasma glucose. HDL-C=high-density lipoprotein cholesterol. LDL-C=low-density lipoprotein cholesterol. SE=standard error. SMBG=self-measured blood glucose.



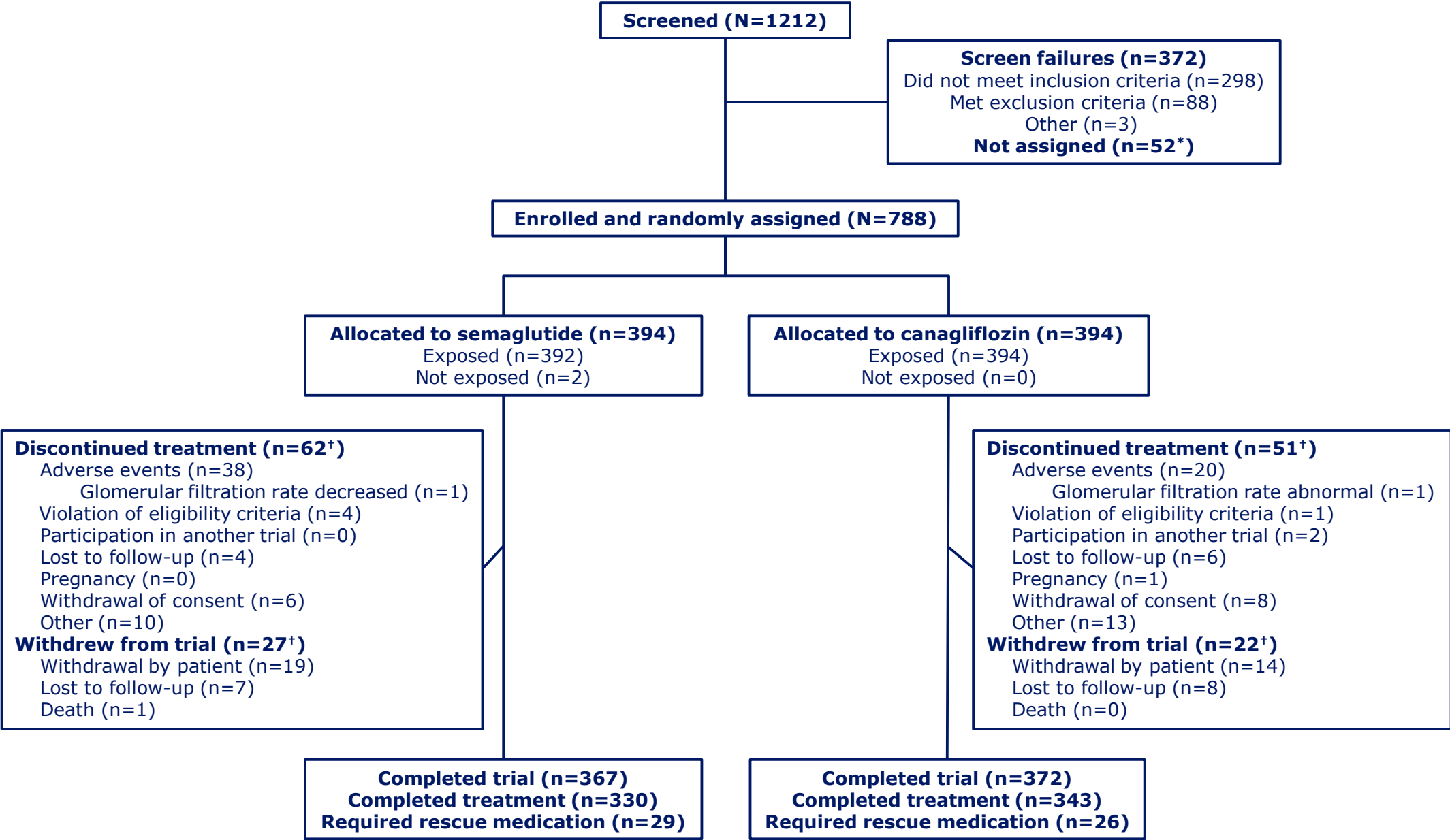
**Table 3: Overview of adverse events**

	Semaglutide 1·0 mg (n=392)			Canagliflozin 300 mg (n=394)		
	n (%)	E	R	n (%)	E	R
All AEs	298 (76)	1189	307·4	283 (71·8)	1138	286·7
Serious AEs	18 (4·6)	30	7·8	21 (5·3)	35	8·8
Fatal AEs*	1 (0·3)	1	0·3	0		
AEs leading to premature treatment discontinuation <sup>†</sup>	38 (9·7)	46	11·9	20 (5·1)	24	6·0
GI AEs leading to premature treatment discontinuation	26 (6·6)	28	7·2	4 (1·0)	4	1·0
GI AEs	184 (46·9)	458	118·4	110 (27·9)	208	52·4
GI AEs occurring in ≥5% of patients						
Nausea	89 (22·7)	127	32·8	26 (6·6)	30	7·6
Diarrhoea	60 (15·3)	95	24·6	37 (9·4)	58	14·6
Vomiting	50 (12·8)	77	19·9	9 (2·3)	9	2·3
Dyspepsia	22 (5·6)	23	5·9	8 (2·0)	8	2·0
Constipation	20 (5·1)	20	5·2	23 (5·8)	23	5·8
Infections and infestations	114 (29·1)	172	44·5	136 (34·5)	241	60·7
Genital and perineal infections	10 (2·6)	11	2·8	48 (12·2)	69	17·4
Hypoglycaemia <sup>‡</sup>	53 (13·5)	122	31·5	32 (8·1)	68	17·1
Severe or BG-confirmed hypoglycaemia <sup>§</sup>	6 (1·5)	25	6·5	5 (1·3)	6	1·5
Severe	1 (0·3)	2	0·5	0		
AEs potentially leading to lower limb amputation <sup>¶</sup>	14 (3·6)	15	3·6	24 (6·1)	27	6·4
Nervous system disorders	8 (2·0)	9	2·1	16 (4·1)	18	4·3

Infections and infestations	0			4 (1.0)	5	1.2
Vascular disorders	3 (0.8)	3	0.7	1 (0.3)	1	0.2
Injury, poisoning and procedural complications (wound)	0			2 (0.5)	2	0.5
Skin and subcutaneous tissue disorders (skin ulcer)	2 (0.5)	2	0.5	0		
Metabolism and nutrition (dehydration)	0			1 (0.3)	1	0.2
Musculoskeletal and connective tissue (osteitis)	1 (0.3)	1	0.2	0		
Other AEs of clinical interest**						
Diabetic retinopathy	9 (2.3)	10	2.4	15 (3.8)	16	3.8
Medication errors and overdose	8 (2.0)	8	2.1	2 (0.5)	2	0.5
Acute renal failure	4 (1.0)	4	1.0	0		
Malignant neoplasms	2 (0.5)	3	0.7	4 (1.0)	4	0.9

\*One (0.3%) sudden cardiac death (confirmed by the Event Adjudication Committee) occurred in the semaglutide 1.0 mg treatment group on trial day 369. This was considered unlikely to be caused by treatment. †Of the AEs leading to premature treatment discontinuation, with semaglutide (n=38 patients): 26 were due to GI disorders; 5 were due to investigations; 4 were due to metabolism and nutrition disorders; 2 were due to nervous system disorders; and 1 was due to each of the following: urinary tract infection, malaise, ureterolithiasis, feeling of despair, palpitations, and back pain; with canagliflozin (n=20 patients): 6 were due to infections and infestation; 4 were due to GI disorders; 3 were due to skin and subcutaneous tissue disorders; 2 were due to each of the following: investigations, general disorders and administration site conditions, and renal and urinary disorders; and 1 was due to each of the following: motor dysfunction, irritability, vertigo, vulvovaginal pruritus and epistaxis. ‡ADA classification (<3.9 mmol/L [<70 mg/dL]). §Severe or BG-confirmed symptomatic hypoglycaemia: an episode that is severe according to the ADA classification or BG-confirmed by a plasma glucose value (<3.1 mmol/L [56 mg/dL]) with symptoms consistent with hypoglycaemia. ¶A signal of increased risk of lower limb amputations has been associated with the use of canagliflozin. While the review of this risk by the health authorities is ongoing, participants at risk were excluded from this trial and assessment of leg and foot was required at every site visit. AEs are shown by system organ class and preferred term, according to a pre-defined MedDRA search. \*\*AEs are based on a pre-defined MedDRA search. %=percentage of patients experiencing at least one event. ADA=American Diabetes Association. AE=adverse event. BG=blood glucose. E=number of events. GI=gastrointestinal. MedDRA=Medical Dictionary for Regulatory Activities. N=number of patients experiencing at least one event. R=event rate per 100 exposure-years.

Figure 1  
**Figure 1. SUSTAIN 8 patient disposition**



# Figure 2A. Estimated mean HbA<sub>1c</sub> by week and change from baseline at week 52

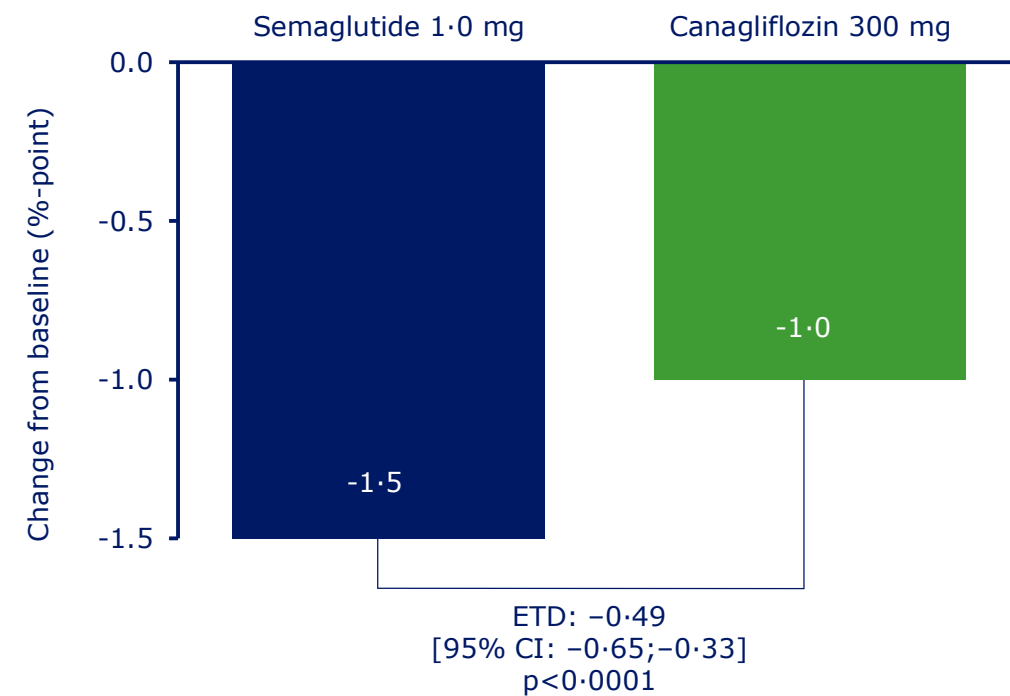
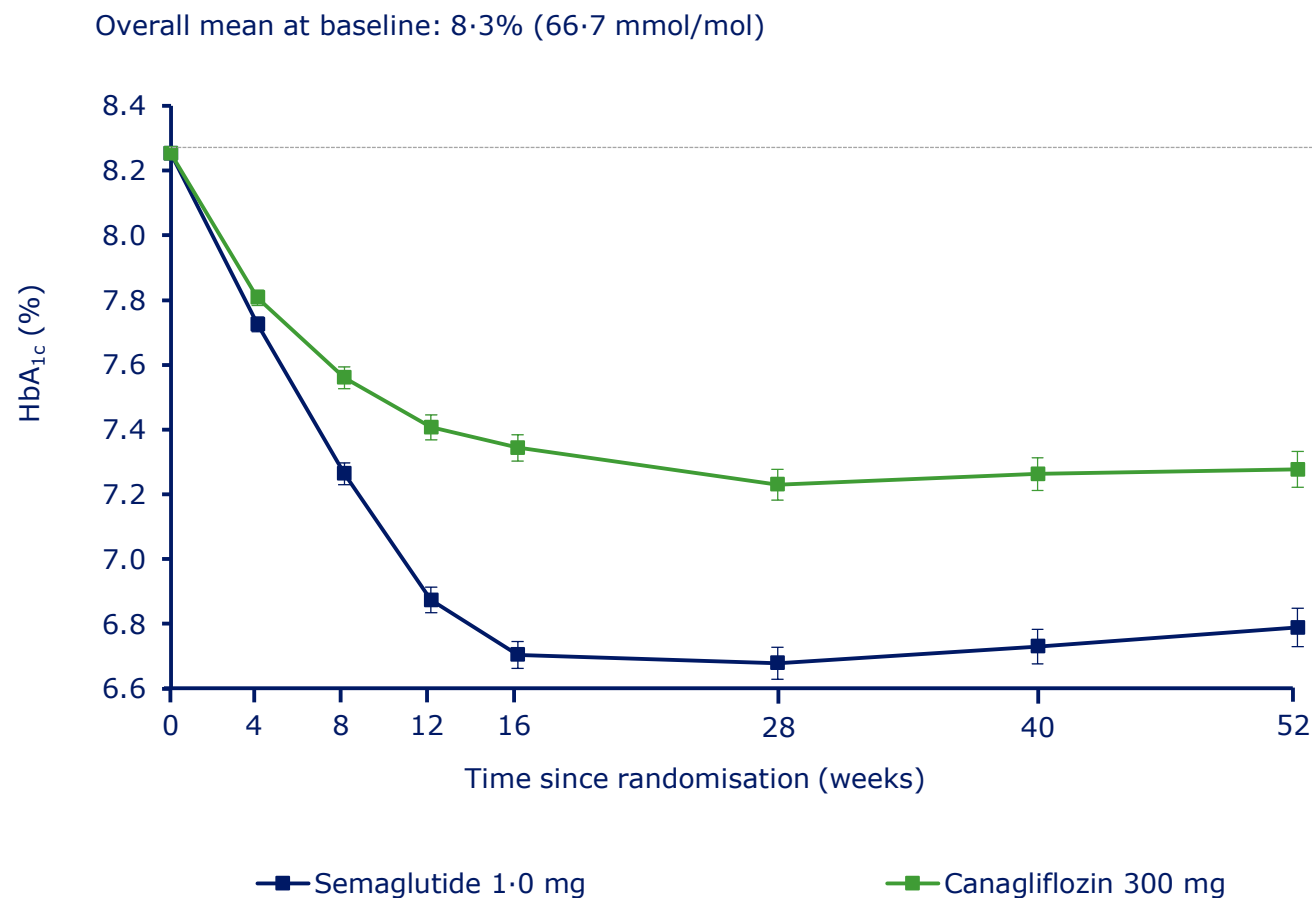
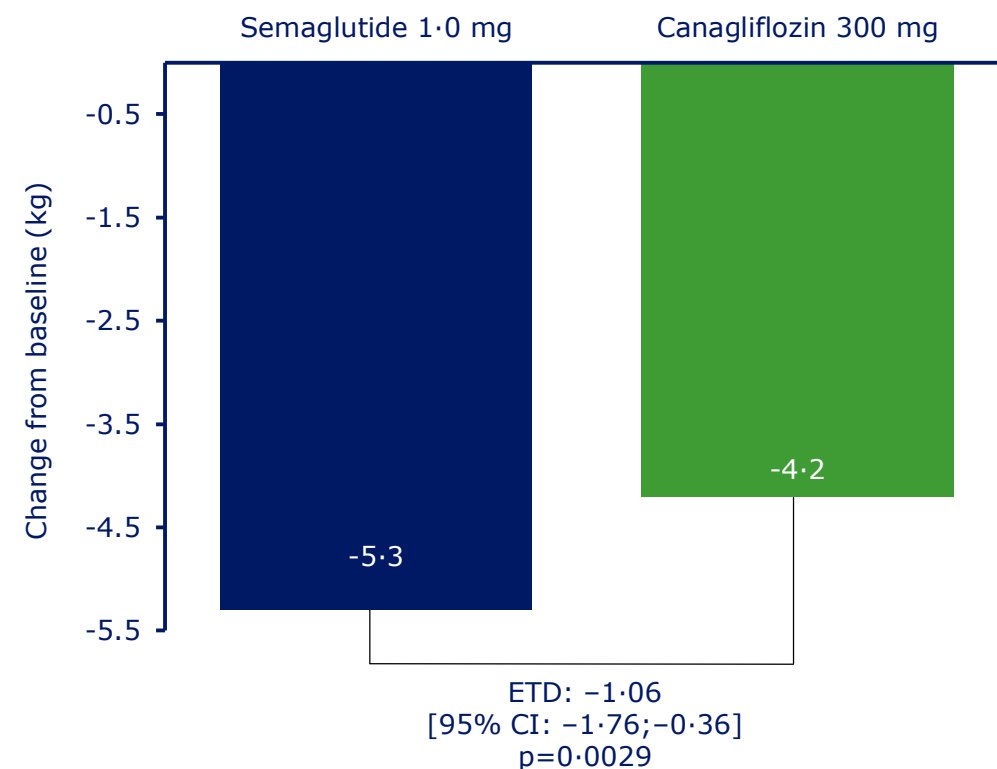
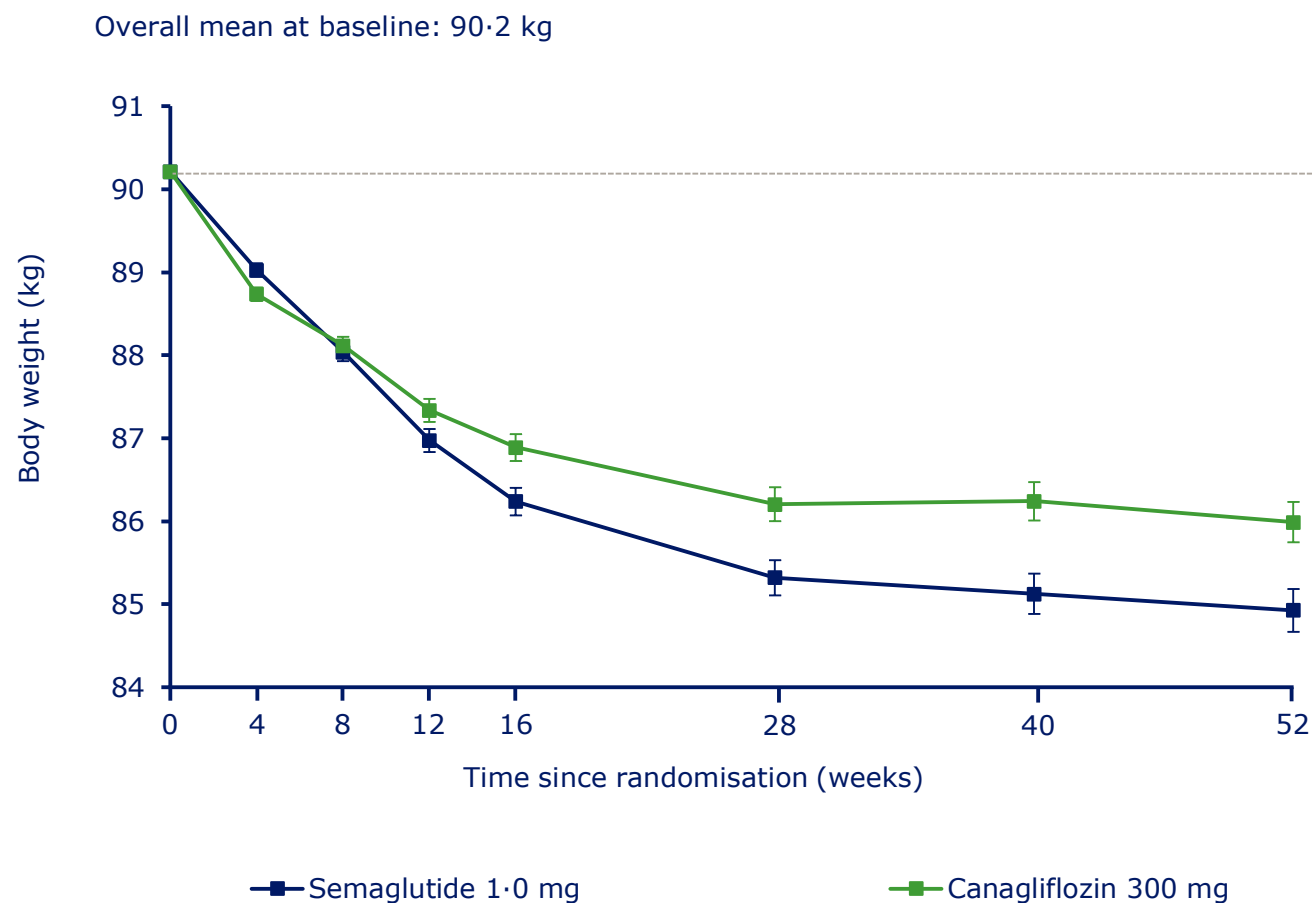


Figure 2B

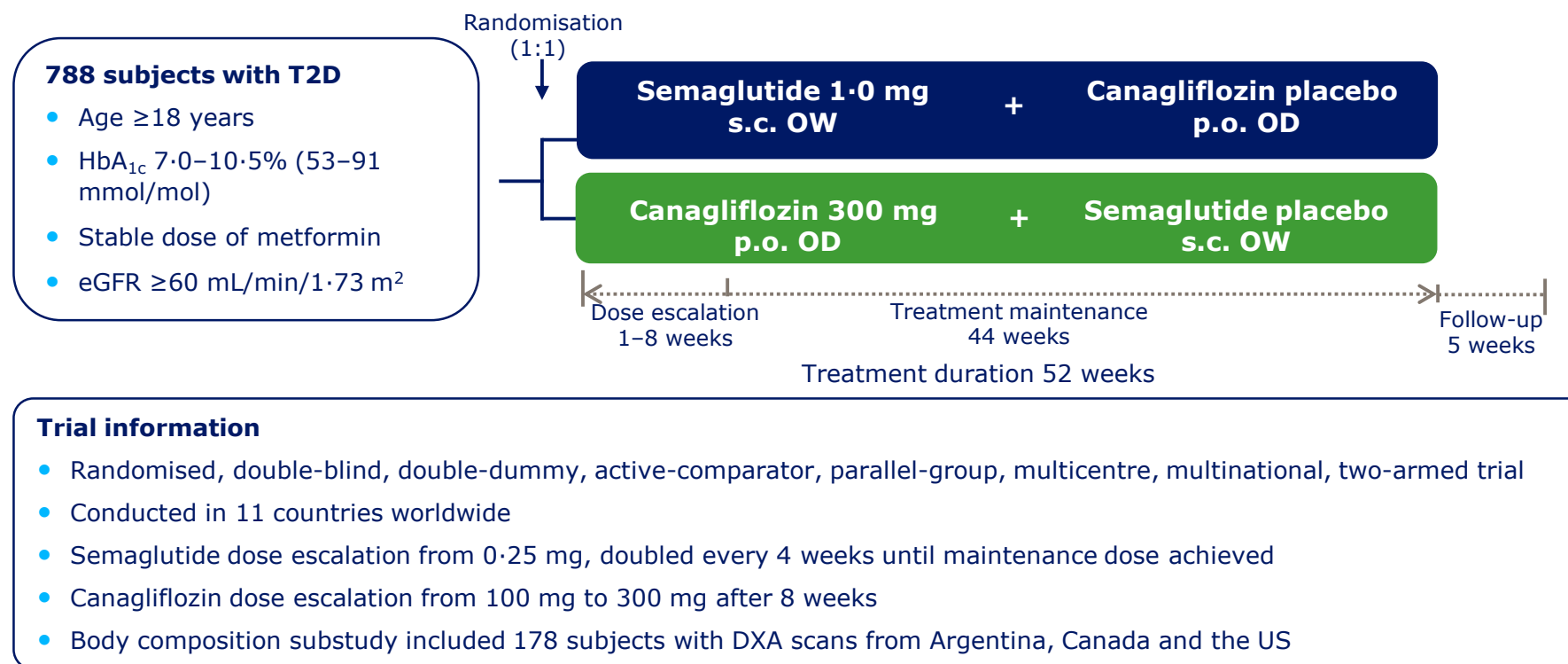
## 2B. Estimated mean body weight by week and change from baseline at week 52



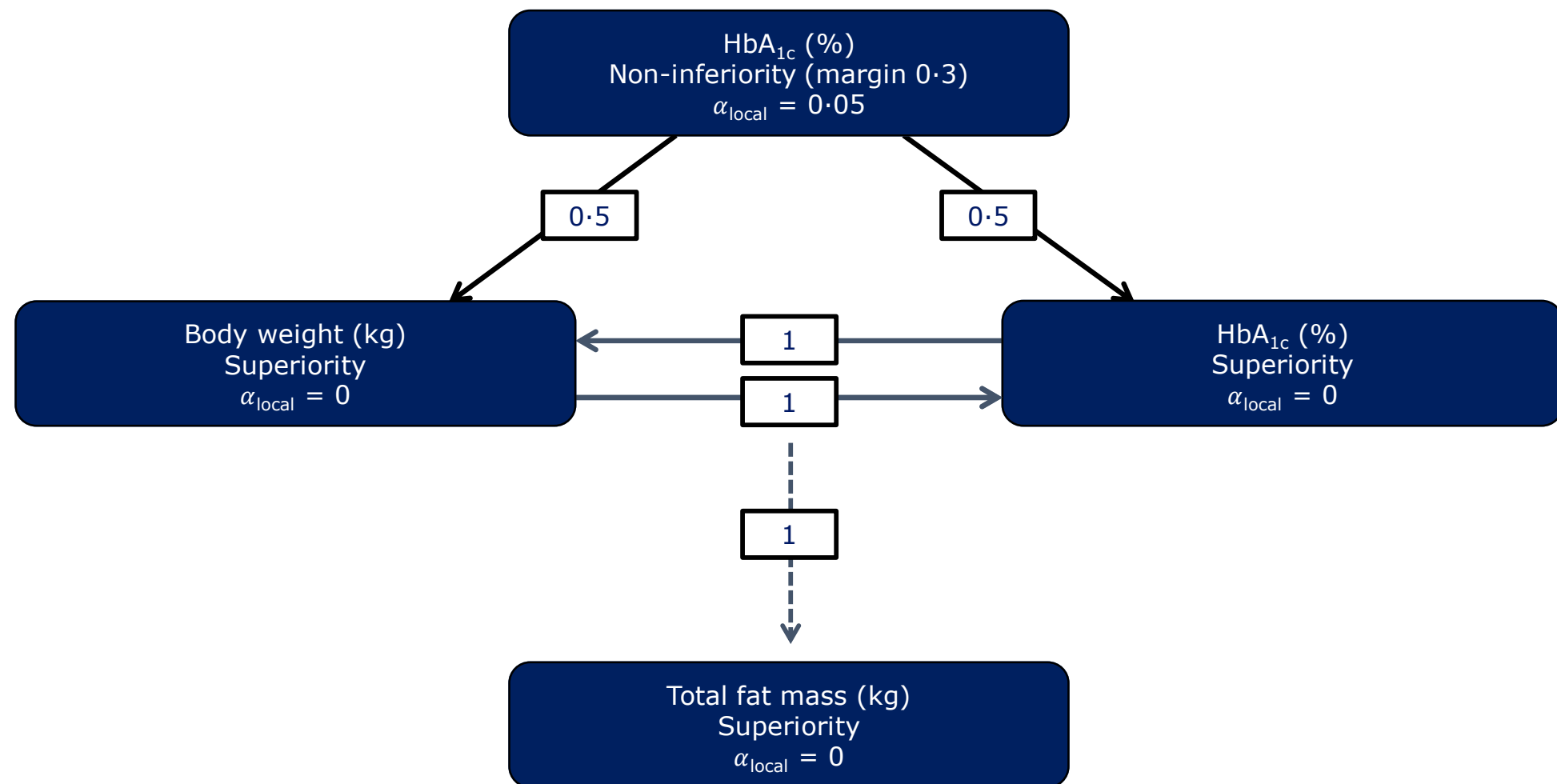
Appendix

[Click here to download Necessary Additional Data: Lingvay et al\\_SUSTAIN 8 appendix.pdf](#)

# Appendix Figure 1. SUSTAIN 8 trial design

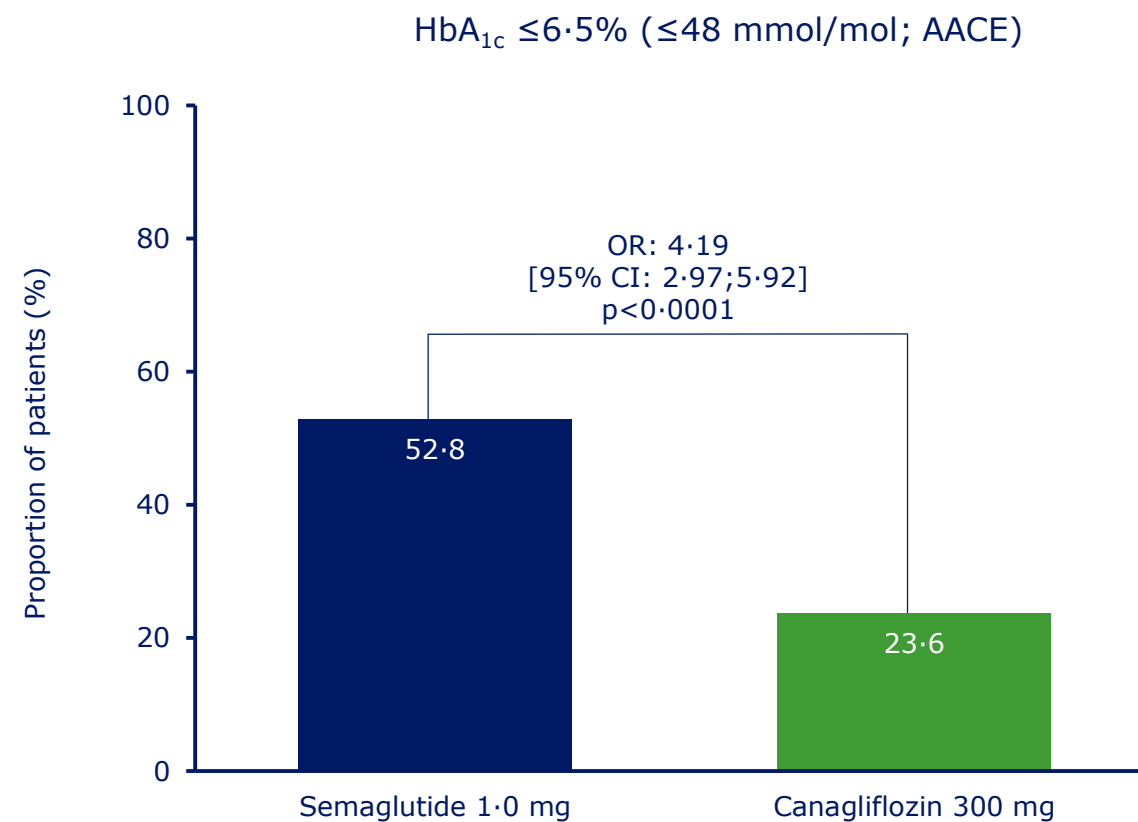
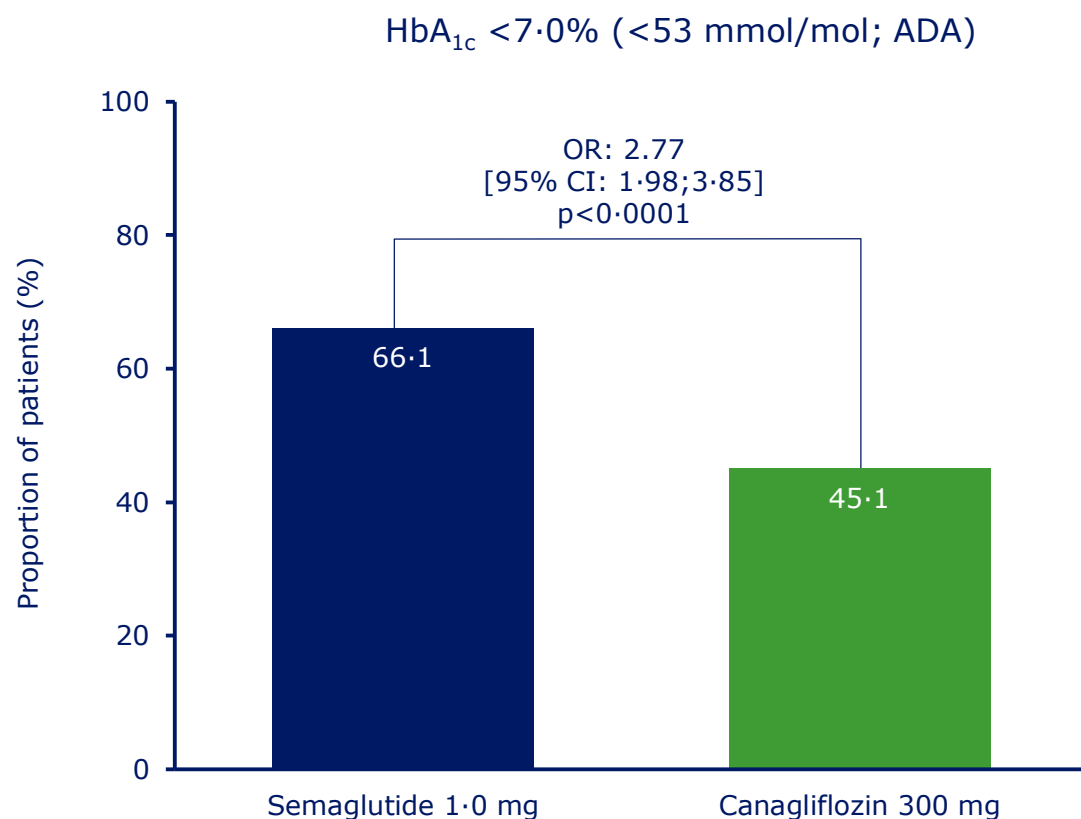


# Appendix Figure 2. Graphical illustration of the closed-testing procedure

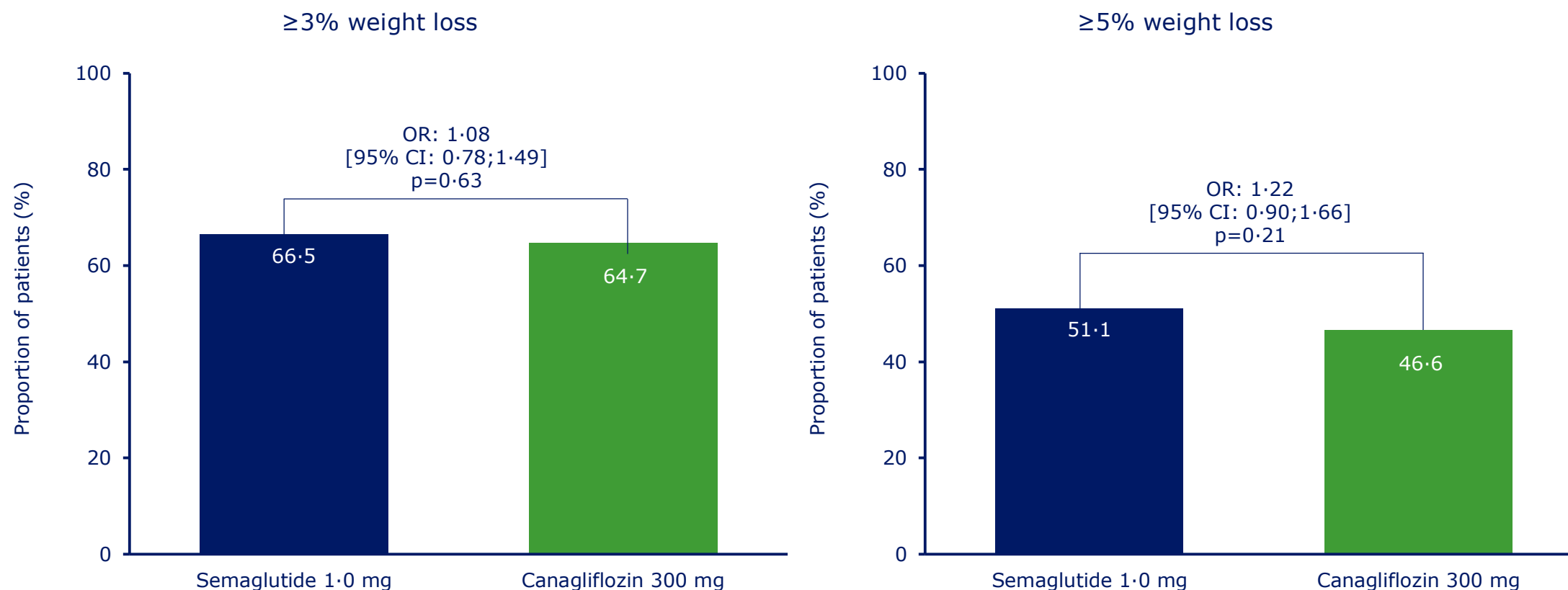




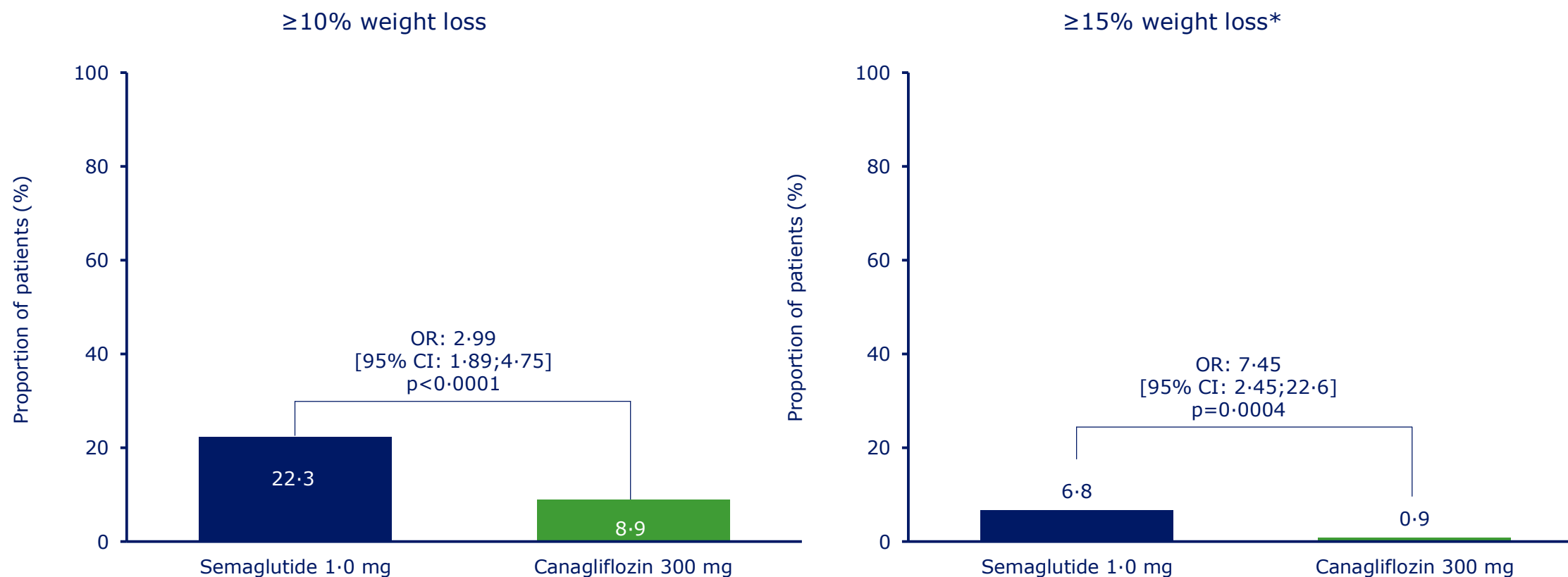
# Appendix Figure 3A. Proportion of patients achieving HbA<sub>1c</sub> targets



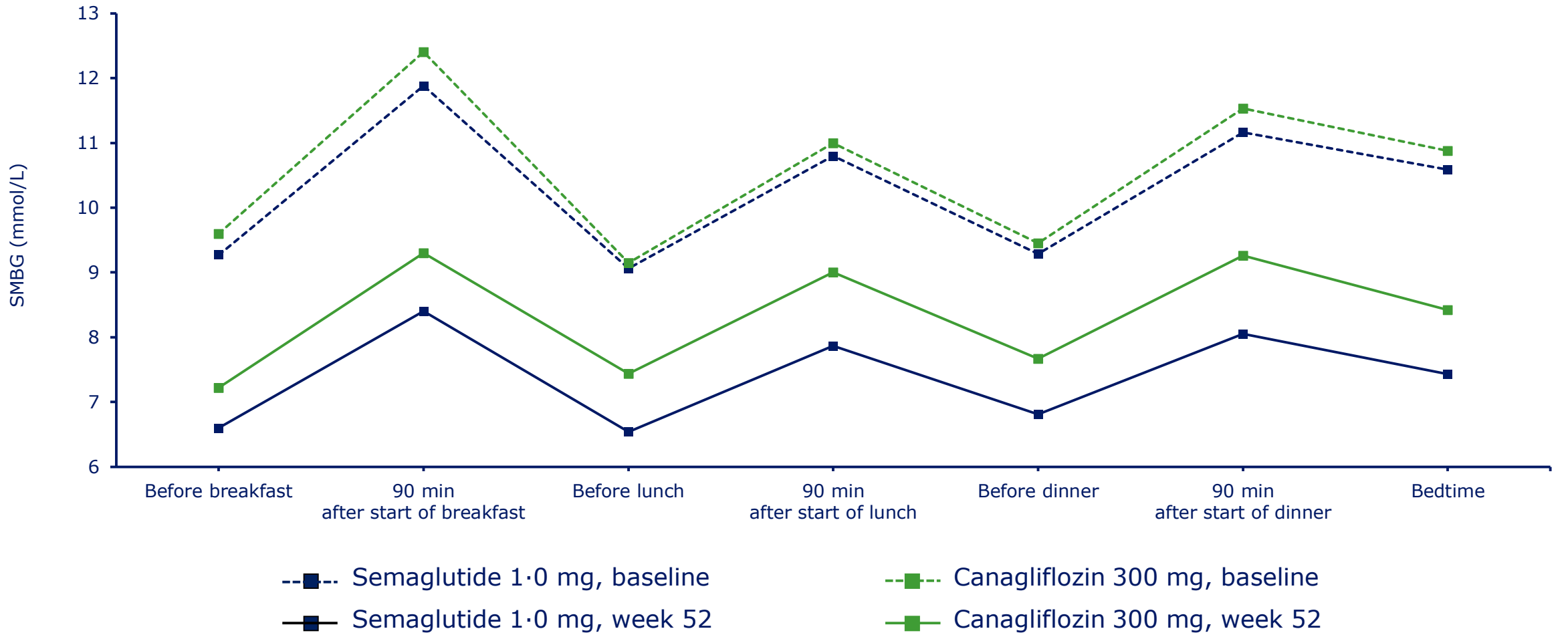
# Appendix Figure 3B. Proportion of patients achieving weight loss responses



# Appendix Figure 3B. Proportion of patients achieving weight loss responses

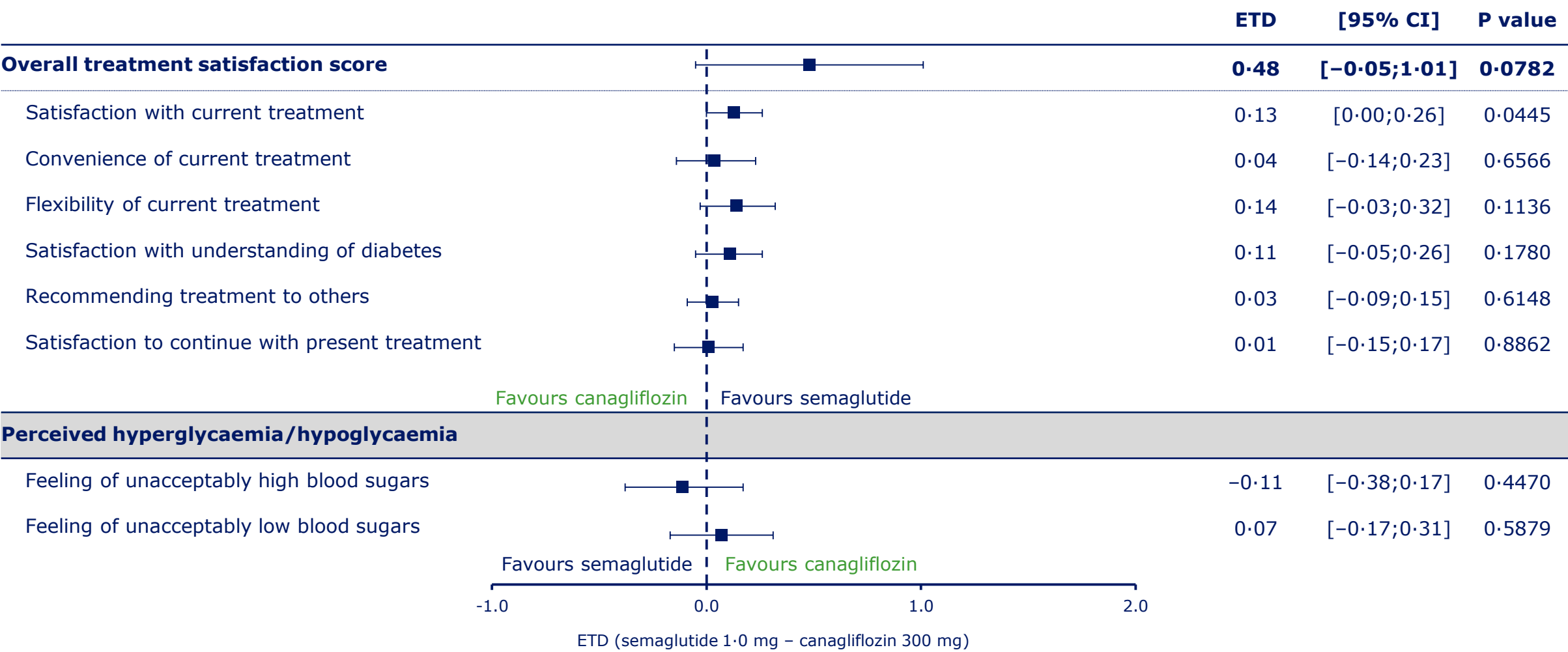


# Appendix Figure 4: Observed mean 7-point self-monitored blood glucose at baseline and week 52

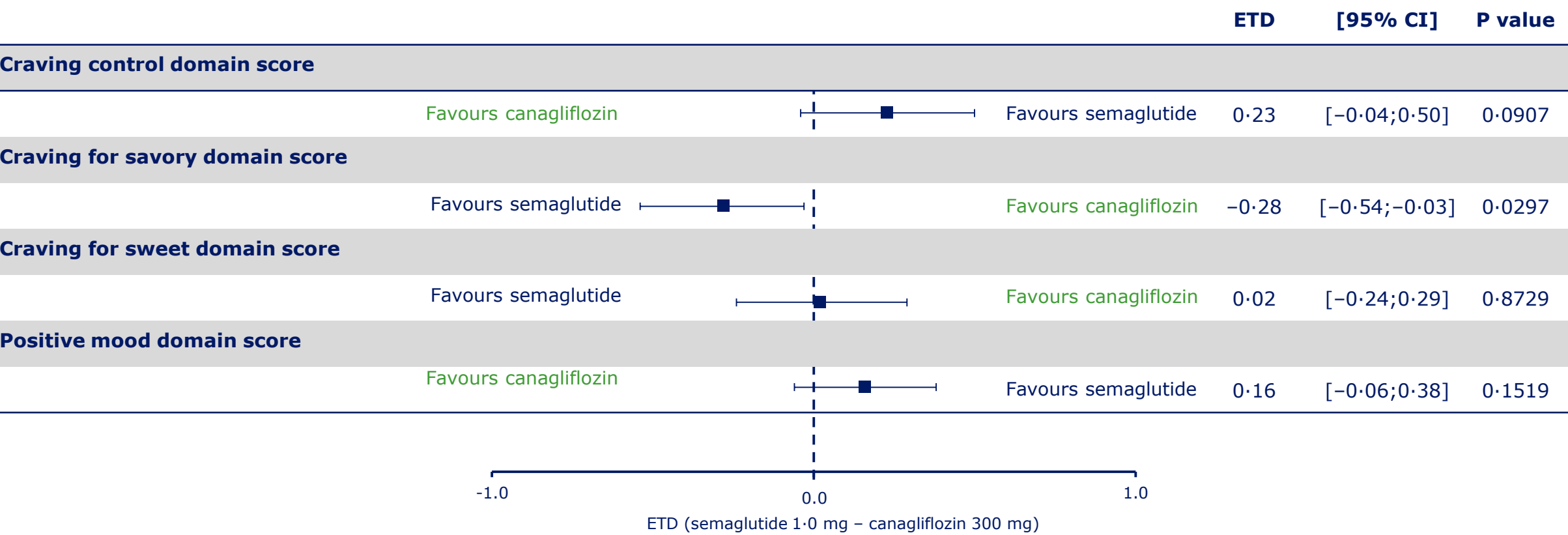


'On-treatment without rescue medication' data. SMBG assessed using glucose meter as plasma equivalent values of capillary whole-blood glucose. SMBG, self-measured blood glucose.

Appendix Figure 5. Change in Diabetes Treatment Satisfaction Questionnaire: short form scores estimated treatment difference at week 52



# Appendix Figure 6. Change in Control of Eating Questionnaire domain scores estimated treatment difference at week 52



ETD, estimated treatment difference.



# CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5,6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6, Table 2 in appendix
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7, Table 3 in appendix
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
<b>Results</b>			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	9, Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9,10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11
<b>Discussion</b>			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12,13
<b>Other information</b>			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	Submitted with paper
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	8,16



\*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).

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July 2019

Dear Editorial Office, *The Lancet Diabetes & Endocrinology*,

I permit Dr Ildiko Lingvay et al. to list my name in the acknowledgments section of their manuscript and I have seen a copy of the manuscript, titled 'Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in subjects with type 2 diabetes (SUSTAIN 8): a double-blind, randomized, controlled trial'.

Yours sincerely,

A handwritten signature in black ink, appearing to be 'SV' followed by a long horizontal flourish.

Sherri Vanderveen

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July 2019

Dear Editorial Office, *Lancet Diabetes and Endocrinology*,

I permit Dr Ildiko Lingvay et al. to list my name in the acknowledgments section of their manuscript and I have seen a copy of the manuscript, titled 'Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in subjects with type 2 diabetes (SUSTAIN 8): a double-blind, randomized, controlled trial'.

Yours sincerely,



Anna Sandberg, MMSc  
Senior Global HEOR Manager

# GLP-1RA VS SGLT-2i IN TYPE 2 DIABETES

HOW DO THEY  
COMPARE?

Lingvay et al. *Lancet Diabetes Endocrinol* 2019.


## SUSTAIN 8


### AIM

Compare the efficacy of  
semaglutide 1.0 mg OW and  
canagliflozin 300 mg OD

### METHODS

 Randomised,  
double-blind,  
multicentre trial  
in 11 countries









 Semaglutide  
1.0 mg OW s.c.  
vs oral canagliflozin  
300 mg OD

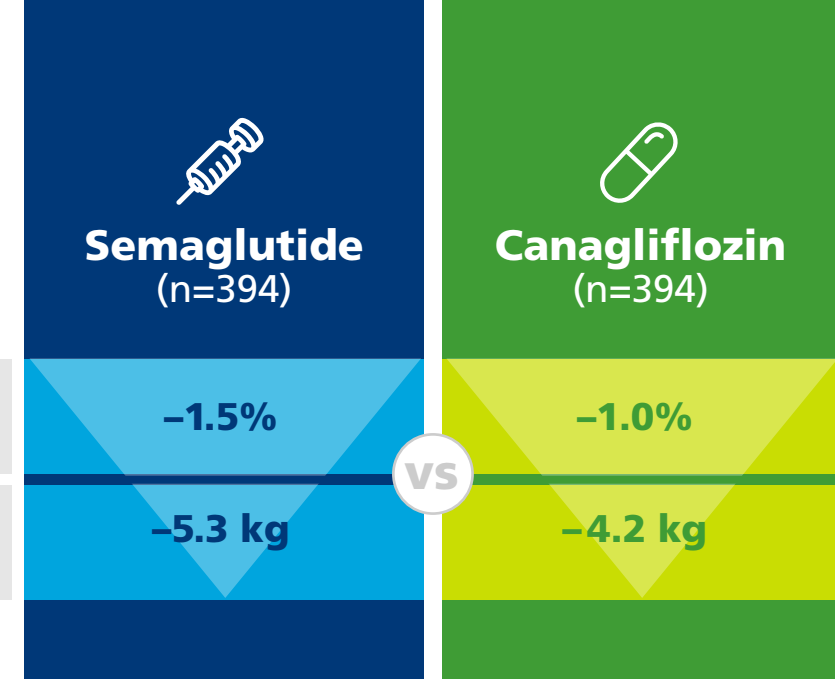
 788 adults  
with uncontrolled T2D  
(HbA<sub>1c</sub>: 7.0–10.5%)  
on metformin

### RESULTS

HbA <sub>1c</sub>	ETD [95% CI]: −0.49% [−0.65;−0.33]; <b>p&lt;0.0001</b>
Weight	ETD [95% CI]: −1.06 kg [−1.76;−0.36]; <b>p&lt;0.003</b>

### SAFETY

Serious AEs	 4.6%	 5.3%
AEs leading to premature treatment discontinuation	 9.7%	 5.1%
GI AEs	 46.9%	 27.9%
Genitourinary infections	 2.6%	 12.2%



### CONCLUSION

Semaglutide was  
**superior** to canagliflozin  
in reducing HbA<sub>1c</sub> and  
body weight in adults  
with T2D

AE, adverse event; CI, confidence interval;  
ETD, estimated treatment difference; GI, gastrointestinal;  
GLP-1RA, glucagon-like peptide-1 receptor agonist;  
OD, once daily; OW, once weekly;  
s.c., subcutaneous; SGLT-2i, sodium–glucose  
cotransporter-2 inhibitor; T2D, type 2 diabetes.

Protocol  
Trial ID:NN9535-4270  
UTN:U1111-1180-3651  
EudraCT no.:2016-000989-35

~~CONFIDENTIAL~~

Date:	19 December 2016
Version:	3.0
Status:	Final
Page:	1 of 118

**Novo Nordisk**

# Protocol

**Trial ID: NN9535-4270**

**Protocol final version 2.0, dated 17 October 2016, including:  
Protocol amendment 01 Global, dated 16 December 2016**

## **SUSTAIN 8 – semaglutide versus canagliflozin**

### **Efficacy and safety of semaglutide versus canagliflozin as add-on to metformin in subjects with type 2 diabetes**

*Redacted protocol  
Includes redaction of personal identifiable information only.*

**Trial phase: 3b**

#### **Protocol originator**

[REDACTED], [REDACTED]

Trial Operations 1, Semaglutide Diabetes & Diabetes Outcomes

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Appendix A Monitoring of Calcitonin

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## List of abbreviations

ADA	American Diabetes Association
AACE	American Association of Clinical Endocrinologists
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
BMI	body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLAE	clinical laboratory adverse event
CoEQ	Control of Eating Questionnaire
CVOT	Cardio Vascular Outcome Trial
DFU	direction for use
DPP-4	ubiquitous dipeptidyl peptidase
DTSQs	Diabetes Treatment Satisfaction Questionnaire, short form
DKA	Diabetic Ketoacidosis
DUN	dispensing unit number
DXA	dual X-ray absorptiometry
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ePRO	electronic patient reported outcome
EMA	European Medicines Agency

Exenatide ER	exenatide extended release
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
HbA <sub>1c</sub>	glycosylated haemoglobin
hCG	human chorionic gonadotrophin
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IgE	immunoglobulin E
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
i.v.	Intravenous
LDL	low-density lipoprotein

LLOQ	lower limit of qualification
LOCF	Last observation carried forward
LPFV	last patient first visit
LPLV	last patient last visit
MACE	major adverse cardiac events
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MEN 2	Multipel endokrin neoplasi typ 2
MI	Myocardial infarction
MMRM	Mixed Model for Repeated Measurements
NIMP	non-investigational medicinal products
NOAEL	no observable adverse event effect level
NYHA	New York Heart Association
OAD	oral antidiabetic drug
OW	Once weekly
P	phone contact
PG	plasma glucose
PK	Pharmacokinetics
PMM	Pattern mixture model
PP	per protocol

PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis set
s.c.	subcutaneous(ly)
SF-36v2 <sup>TM</sup>	Short form healthy survey
SDV	source data verification
SIF	safety information form
SGLT-2	Sodium-glucose co-transporter-2
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T2D	Type 2 diabetes mellitus
TMM	Trial Materials Manual
UNL	upper normal limit
UNR	upper normal range
UTN	Universal Trial Number

# 1 Summary

## Objective(s) and endpoint(s):

### Primary objective

To compare the effect of once-weekly (OW) dosing of subcutaneous semaglutide (1.0 mg) versus once-daily dosing of oral canagliflozin (300 mg) on glycaemic control in subjects with type 2 diabetes (T2D) on a background treatment of metformin.

### Secondary objectives

To compare the effects of semaglutide s.c. 1.0 mg once-weekly versus canagliflozin 300 mg once-daily after 52 weeks of treatment in subjects with T2D with regards to:

- Weight management
- Other parameters of effect, safety and Patient Reported Outcomes

### Endpoint(s)

#### Primary endpoint

- Change from baseline to week 52 in HbA<sub>1c</sub>

### Supportive secondary efficacy endpoints

Change from baseline to week 52 in:

- Fasting Plasma Glucose (FPG)\*
- Systolic and diastolic blood pressure\*
- Diabetes Treatment Satisfaction Questionnaire (DTSQ)\*: Treatment satisfaction score (sum of 6 of 8 items) and the 8 items separately

### Trial design:

This is a 52-week, confirmatory, randomised, double-blind, double dummy, active-controlled, multicentre, multinational, two-arm, parallel-group trial.

Subjects with type 2 diabetes inadequately controlled with metformin alone will after approximately 2 weeks screening period be randomised in a 1:1 manner to receive either a dose of 1.0 mg semaglutide once-weekly or 300 mg canagliflozin once-daily.

After a period of approximately 52 weeks in total, all subjects enter a follow up period of 5 weeks ended by a follow-up visit. Total trial duration for the individual subjects will be approximately 59 weeks.

### Trial population:

A planned total number of 784 subjects will be randomised in a 1:1 manner.



## **Inclusion criteria**

For an eligible subject, all inclusion criteria must be answered “yes”.

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age  $\geq 18$  years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus (T2D).
4. HbA<sub>1c</sub> of 7.0-10.5% (53-91 mmol/mol, both inclusive).
5. Stable daily dose of metformin ( $\geq 1500$  mg or maximum tolerated dose as documented in the subject medical record and in compliance with current local label) for at least 90 days prior to the day of screening.

## **Exclusion criteria**

For an eligible subject, all exclusion criteria must be answered “no”.

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days prior to the day of screening.
5. Any disorder which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
6. Subject with alanine aminotransferase (ALT)  $> 2.5 \times$  upper normal limit (UNL).
7. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
8. History or presence of pancreatitis (acute or chronic).
9. History of diabetic ketoacidosis (DKA).
10. Any of the following: myocardial infarction (MI), stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
11. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
12. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
13. Renal impairment measured as eGFR  $< 60$  ml/min/1.73 m<sup>2</sup> as defined by Kidney Disease Improving global outcomes (KDIGO 2012)<sup>1</sup> classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening.
14. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed.

15. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.
16. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ is allowed.
17. Medical history of diabetes-related lower limb amputations or signs of critical lower limb ischemia, (e.g. skin ulcer, osteomyelitis, or gangrene) within the last 26 weeks prior to screening.

**Assessments:**

- Glucose metabolism (HbA<sub>1c</sub>, fasting plasma glucose)
- Body measurements (weight (kg), body mass index (BMI), waist circumference, total fat mass (kg) and total lean mass measured by DXA in a sub-population)
- Blood pressure
- Fasting blood lipids (total cholesterol, LDL, HDL and triglycerides)
- Self-measured plasma glucose (7-point profile)
- Patient reported outcomes
- Adverse events and serious adverse events
- Hypoglycaemic episodes
- Biochemistry and haematology
- Pulse
- Calcitonin and creatinine
- Physical examination
- Electrocardiogram
- Dilated fundoscopy/fundophotography

**Trial product(s):**

The following trial products will be provided by Novo Nordisk A/S, Denmark.

Investigational medicinal products:

- Test product: Semaglutide 1.34mg/ml, solution for injection, 1.5 mL prefilled PDS290 pen-injector
- Reference therapy: Canagliflozin 100 mg/300 mg, tablets

## 2 Flow chart

Trial Periods		Screening	Randomisation	Treatment						End of Treatment	Follow-up	End of treatment, Premature discontinuation	Follow-up	
Visit (V)/ phone contact (P)		V1	V2	V3	V4	P5	V6	V7	V8	V9	V10	P11	V10A	P11A
Timing of visit (weeks)		-2	0	4	8	10	12	16	28	40	52	57		
Visit window (days)		±7		±3	±3	±3	±7	±7	±7	±7	±7	+7		
SUBJECT RELATED INFO/ASSESSMENTS	Section													
Informed consent	<a href="#">18.3</a>	x												
In/exclusion criteria	<a href="#">6.2, 6.3</a>	x	x											
Randomisation	<a href="#">6.4</a>		x											
Withdrawal criteria	<a href="#">6.7</a>			x	x	x	x	x	x	x	x		x	
Concomitant illness	<a href="#">8.2.4</a>	x												
Concomitant medication	<a href="#">8.2.5</a>	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	<a href="#">8.2.1</a>	x												
Hypoglycaemia unawareness	<a href="#">8.2.3</a>	x												
Diagnosis of diabetes	<a href="#">8.2.2</a>	x												
Diabetes history and diabetes complications	<a href="#">8.2.2</a>	x												
Medical history	<a href="#">8.2.4</a>	x												
Tobacco use	<a href="#">8.2.7</a>	x												
EFFICACY														
Height	<a href="#">8.3.1</a>		x											
Body weight	<a href="#">8.3.1</a>		x	x	x		x	x	x	x	x		x	
BMI	<a href="#">8.3.1</a>		x	x	x		x	x	x	x	x		x	
Waist circumference	<a href="#">8.3.1</a>		x						x		x		x	
PRO questionnaires	<a href="#">8.6.2</a>		x						x		x		x	

Trial Periods		Screening	Randomisation	Treatment						End of Treatment	Follow-up	End of treatment, Premature discontinuation	Follow-up	
Visit (V)/ phone contact (P)		V1	V2	V3	V4	P5	V6	V7	V8	V9	V10	P11	V10A	P11A
Timing of visit (weeks)		-2	0	4	8	10	12	16	28	40	52	57		
Visit window (days)		±7		±3	±3	±3	±7	±7	±7	±7	±7	+7		
SUBJECT RELATED INFO/ASSESSMENTS														
EFFICACY cont.	Section													
Systolic blood pressure	<a href="#">8.3.3</a>	x	x	x	x		x	x	x	x	x		x	
Diastolic blood pressure	<a href="#">8.3.3</a>	x	x	x	x		x	x	x	x	x		x	
Fasting plasma glucose	<a href="#">8.5.1</a>		x	x	x		x	x	x	x	x		x	
HbA <sub>1c</sub>	<a href="#">8.5.1</a>	x	x	x	x		x	x	x	x	x		x	
Lipids	<a href="#">8.5.1</a>		x						x		x		x	
7-point profile	<a href="#">8.3.5</a>		x						x		x		x	
DXA scan	<a href="#">8.3.6</a>	x									x		x	
SAFETY														
Hypoglycaemic episodes	<a href="#">8.4.6</a>		x	x	x	x	x	x	x	x	x	x	x	x
ECG	<a href="#">8.4.3</a>		x						x		x		x	
Eye examination	<a href="#">8.4.4</a>		x								x		x	
Physical examination	<a href="#">8.4.1</a>	x							x		x		x	
-Legs and Feet examination	<a href="#">8.4.1</a>	x	x	x	x		x	x	x	x	x		x	
Pulse, sitting	<a href="#">8.4.2</a>	x	x	x	x		x	x	x	x	x		x	
Biochemistry	<a href="#">8.5.2</a>	x	x	x	x		x	x	x	x	x		x	
Creatinine (including eGFR)	<a href="#">8.5.2</a>	x	x	x	x		x	x	x	x	x		x	
Haematology	<a href="#">8.5.2</a>		x	x	x		x	x	x	x	x		x	
Pregnancy test	<a href="#">8.5.2</a>	x	x						x		x		x	
Adverse events	<a href="#">12.1.1</a>		x	x	x	x	x	x	x	x	x	x	x	x
Calcitonin	<a href="#">8.5.2</a>		x						x		x		x	

Trial Periods		Screening	Randomisation	Treatment						End of Treatment	Follow-up	End of treatment, Premature discontinuation	Follow-up	
Visit (V)/ phone contact (P)		V1	V2	V3	V4	P5	V6	V7	V8	V9	V10	P11	V10A	P11A
Timing of visit (weeks)		-2	0	4	8	10	12	16	28	40	52	57		
Visit window (days)		±7		±3	±3	±3	±7	±7	±7	±7	±7	+7		
SUBJECT RELATED INFO/ASSESSMENTS														
TRIAL MATERIAL cont.	Section													
Dispensing visit			x	x	x		x	x	x	x				
Drug accountability				x	x		x	x	x	x	x		x	
IWRS call	<a href="#">10</a>	x	x	x	x		x	x	x	x	x		x	
REMINDERS														
Fasting visits	<a href="#">8.1.5</a>		x	x	x		x	x	x	x	x		x	
Hand-out direction for use (DFU)			x											
End of treatment											x		x	
End of trial												x <sup>a</sup>		
Hand-out and instruct on BG meter use		x												
Re-training on the BG meter use			x											
Training in trial product and pen handling			x	x										
Hand out ID card		x												
Hand out and instruct in diary	<a href="#">8.6.1</a>	x	x	x	x		x	x	x	x				
Collect and review diary			x	x	x		x	x	x	x	x		x	

<sup>a</sup> If premature discontinuation, End of Treatment form must be filled-in when the discontinuation happens and End of Trial form at scheduled visit P11. If a subject completes both the treatment and the trial at scheduled time, the End of Treatment form must be filled at V10 and End of Trial form to be filled in at P11. In case of subject withdrawal, both End of Treatment form and End of Trial form must be filled-in at the time they withdraw from the trial.

### 3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP<sup>2</sup> and applicable regulatory requirements, and in accordance with the Declaration of Helsinki<sup>3</sup>.

*For Mexico only: The above will include the following responsibilities for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility:*

- a) *Investigation follow-up*
- b) *Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Subject;*
- c) *Timely compliance of the terms in which the authorization of a research for health in human beings had been issued;*
- d) *To present in a timely manner the information required by the Health Authority*

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

#### 3.1 Background information

##### 3.1.1 Type 2 diabetes

Type 2 diabetes (T2D) is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver<sup>4</sup>.

Optimal glycaemic control is the treatment goal in subjects with T2D in order to prevent long-term complications associated with chronic hyperglycaemia<sup>5</sup>. Despite the availability of several antidiabetic drugs, a significant proportion of subjects with T2D do not achieve the recommended blood glucose (BG) target levels<sup>6,7</sup>.

##### 3.1.2 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone with a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets<sup>8,9</sup>. Subjects with T2D have a decreased incretin effect<sup>10-13</sup>. However, the insulinotropic action of GLP-1 and thus, the ability to lower blood glucose (BG) levels, is preserved when GLP-1 is administered at supraphysiological levels<sup>14</sup>. In addition, supraphysiological levels of GLP-1 induce reduction in body weight<sup>15</sup>. GLP-1 is a physiological regulator of appetite and food intake and GLP-1 receptors are present in several areas of the brain involved in appetite regulation<sup>16,17</sup>. Physiologically, GLP-1 also has a pronounced inhibitory effect on gastric emptying; however this effect seems to diminish

upon chronic stimulation of the GLP-1 receptor<sup>15-17</sup>. These mechanisms of action make glucagon-like peptide-1 receptor agonists (GLP-1RAs) an attractive pharmacological treatment for T2D<sup>18-20</sup>.

### **3.1.3 Semaglutide**

Semaglutide is a potent human GLP-1 analogue with a pharmacokinetic (PK) profile suitable for once-weekly subcutaneous (s.c.) administration. It is structurally similar to liraglutide (Victoza<sup>®</sup>), a once-daily GLP-1RA developed by Novo Nordisk and approved worldwide for the treatment of T2D. The extended half-life of the semaglutide molecule is primarily obtained due to binding to albumin, which is facilitated by a large fatty acid derived chemical moiety attached to the lysine in position 26. The specific modifications in the molecule are: 1) a modification in position 8 (alanine to 2-aminoisobutyric acid) of the peptide backbone to increase stability against DPP-4, and a change in position 34 from a lysine to an arginine to limit the options for acylation to the one remaining lysine in the sequence; 2) a large hydrophilic spacer between the lysine in position 26 and the gamma glutamate where the fatty acid is attached; 3) a C18 fatty di-acid with a terminal acidic group<sup>21, 22</sup>. The spacer and the fatty acid both contribute to increased albumin binding, which results in a prolonged half-life of approximately 1 week, making semaglutide suitable for once weekly (OW) s.c. administration.

### **3.1.4 Non-clinical data**

#### **3.1.4.1 Semaglutide**

The nonclinical programme for semaglutide was designed according to the ICH M3<sup>23</sup> guideline to support the clinical development. The standard nonclinical data package required to support phase 3 clinical trials has been completed. In addition, 2-year carcinogenicity studies and a pre- and postnatal development toxicity study have been completed.

Semaglutide is generally well tolerated with expected GLP-1 effects on food intake and body weight being dose limiting in mice, rats and cynomolgus monkeys. Two potential safety issues have been identified and are detailed below.

#### **Thyroid C-cell tumours in rodents**

Thyroid C-cell neoplasia was seen in mice and rat 2-year carcinogenicity studies. Proliferative C-cell changes in rodents are a known effect following GLP-1 receptor activation by GLP-1 receptor agonists. The finding in rodents is caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. Recently published data have shown that the GLP-1 receptor is not expressed in the normal human thyroid, and accordingly, the risk of GLP-1 receptor mediated C-cell changes in humans is considered to be low<sup>24</sup>.

#### **Embryo–foetal development toxicity**

Semaglutide adversely affected embryo–foetal development in the rat by a GLP-1 receptor-mediated impaired function of the inverted yolk sac placenta during a period of gestation when the

rat embryo is entirely dependent on the inverted yolk sac placenta for its nutrient supply. In primates, the yolk sac does not invert to fully enclose the embryo, and it does not come in direct contact with the uterine wall to form a placenta as in rodents. Accordingly, the mechanism by which semaglutide adversely affects embryo-foetal development in the rat, is not likely to be of relevance to humans. Studies in cynomolgus monkeys confirmed that maternal dosing of semaglutide does not affect embryo-foetal development in this species. However, the initial maternal body weight loss caused by the pharmacological effect of semaglutide coincided with increased early pregnancy loss in one of three studies. In cynomolgus monkeys, the overall developmental no observable adverse event effect level (NOAEL) was determined to be 0.015 mg/kg/3 days, which provides an exposure equivalent to the human exposure at 1.0 mg/week based on area under the curve (AUC).

A comprehensive review of results from the nonclinical studies can be found in the current edition of semaglutide (NN9535) Investigator's Brochure (IB),<sup>25</sup> or any updates hereof.

### **3.1.5 Clinical data – semaglutide**

As of 1 August 2016, 16 clinical pharmacology trials (trials 1820, 3679, 3633, 3616, 3819, 4010, 3789, 3652, 3685, 3634, 3687, 3817, 3818, 3684, 3651 and 3635) and 1 phase 2 trial (trial 1821) and 8 phase 3a trials (NN9535-3623, 3624, 3625, 3626, 3627, 3744, 4091, 4092) have been completed with semaglutide s.c.OW.

Clinical pharmacology trials were conducted in healthy subjects, in subjects with T2D, in subjects with obesity and in subjects with renal- and hepatic impairment. Semaglutide phase 3a programme evaluated the efficacy and safety of semaglutide in a broad T2D population and covered the continuum of T2D care. The programme evaluated mono- and combination therapy with antiglycaemic therapies and compared semaglutide with the most important comparators at the time of initiating the phase 3a programme. In addition, the phase 3a programme included a long-term (104-week) cardiovascular outcomes trial (trial 3744) in a T2D population at high risk of cardiovascular events.

#### **3.1.5.1 Pharmacokinetics**

The results from the completed clinical pharmacology trials confirm that semaglutide has PK properties compatible with once-weekly administration, having a flat concentration profile over time, with a median time to maximum concentration ( $t_{\max}$ ) of 36–60 hours post-dosing and an elimination half-life ( $t_{1/2}$ ) of approximately 1 week (149–165 hours). The absolute bioavailability of semaglutide s.c. was estimated to be 89%. The PK properties of semaglutide appear comparable between healthy subjects, subjects with T2D and subjects with renal failure.

Results from drug-interaction studies with warfarin, metformin, atorvastatin and digoxin indicate that no dose adjustment of the co-administered drugs is warranted when administered together with semaglutide. In addition, semaglutide does not decrease the exposure of oral contraceptives and hence, is not anticipated to decrease the effectiveness of oral contraceptives.



### 3.1.5.2 Efficacy

Based on results from the clinical pharmacology trials, semaglutide treatment, compared to placebo, reduced both fasting and postprandial plasma glucose by improving multiple aspects of beta-cell function and by reducing both fasting and postprandial glucagon concentrations, all in a glucose dependent manner. The body weight loss observed with semaglutide was primarily from fat tissue and was considered to be explained by lowered appetite, both in the fasting and postprandial state, and lowered energy intake. In addition, semaglutide improved control of eating and reduced food cravings. Similar to other GLP-1 receptor agonists, semaglutide caused a minor delay of early postprandial gastric emptying.

Both as monotherapy and as combination therapy, semaglutide significantly reduced HbA<sub>1c</sub> and body weight in all phase 3a trials when compared with the trial-specific comparator, including the active comparators sitagliptin, exenatide extended release (exenatide ER) and insulin glargine. In the 5 global phase 3a trials (3623, 3624, 3625, 3626 and 3627), reductions in HbA<sub>1c</sub> and body weight of up to 1.85 %-point and 6.42 kg, respectively, were obtained with semaglutide 1.0 mg. Significantly more subjects with semaglutide versus comparators reached the ADA and AACE-defined treatment targets of an HbA<sub>1c</sub> <7% and ≤6.5%, respectively, and weight loss responses of ≥5% and ≥10%. The superior and clinically relevant beneficial effects of semaglutide on glycaemic control as estimated by change in HbA<sub>1c</sub> were substantiated by improvements in secondary glycaemia-related supportive endpoints.<sup>26-29</sup>

### 3.1.5.3 Safety

Data from the 5 global phase 3a clinical trials (NN9535-3623, 3624, 3625, 3626 and 3627) showed that the safety and tolerability of semaglutide at doses up to 1.0 mg per week and administered for up to 56 weeks of treatment were consistent with other GLP-1RAs. Commonly reported adverse events (AEs) included nausea and vomiting, most of which were mild to moderate in severity. The escalation regimen utilized was associated with good tolerability and low numbers of discontinuation due to AEs. Accordingly, the most frequently reported AEs in subjects with T2D were gastrointestinal (e.g., nausea and vomiting), as were the most frequent AEs leading to premature treatment discontinuation.

Hypoglycaemia occurred infrequently in subjects receiving semaglutide and the events were mainly non-severe. Hypoglycaemic episodes have mainly been observed when semaglutide is combined with SU or insulin. In line with findings for other GLP-1RAs, an increase in heart rate and serum levels of lipase and amylase has also been observed in subjects exposed to semaglutide. As with all protein based pharmaceuticals, subjects treated with semaglutide may develop immunogenic and allergic reactions. However, only few subjects administered semaglutide experienced allergic reactions and injection site reactions. These have mainly been mild and transient of nature; however, more generalised reactions may occur.

The effect of semaglutide on major adverse cardiovascular events (MACE) was evaluated in a T2D population at high risk for CV events, in the cardiovascular outcome trial, SUSTAIN 6 (NN9535-3744)<sup>30</sup>. SUSTAIN 6 trial achieved its primary objective by showing non-inferiority of once-weekly s.c. semaglutide versus placebo on cardiovascular outcomes; moreover, s.c. semaglutide statistically significantly reduced cardiovascular risk versus placebo<sup>30</sup>. In addition, results from the recently completed LEADER® trial (EX2211-3748) showed that treatment with the once daily liraglutide does not increase the risk of MACE as compared to placebo. In fact, treatment with liraglutide reduced the risk of the primary composite outcome consisting of death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke by 13% versus placebo<sup>31</sup>. A post-marketing cardiovascular outcomes trial on canagliflozin (CANVAS) is ongoing and results are expected in Q1 2017, see <https://clinicaltrials.gov/ct2/show/NC01032629>.

The overall safety profile of semaglutide in the SUSTAIN 6 trial (NN9535-3744) was consistent with previous semaglutide clinical studies. However, in this trial, the diabetic retinopathy complications were reported more frequently in the semaglutide-treated subjects compared with placebo. Please see Section [18](#) for more details.

Please see the current edition of semaglutide s.c. (NN9535) IB or any updates hereof for further details<sup>25</sup>.

For an assessment of benefits and risks of the trial, see Section [18.1](#).

### **3.1.6 Canagliflozin**

The selected active comparator in this trial is canagliflozin, a selective inhibitor of the sodium-glucose co-transporter-2 (SGLT-2), which is the predominant transporter responsible for glucose reabsorption from the glomerular filtrate back into the circulation. Inhibition of SGLT-2 reduces BG levels by blocking renal glucose reabsorption, thereby increasing urinary glucose excretion. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on the BG concentration and renal function. Canagliflozin was developed by Janssen Pharmaceuticals and approved in 2013 in the US to improve glycaemic control in adults with T2D.

For further details, please see the current approved label for canagliflozin<sup>32</sup>.

For an assessment of benefits and risks of the trial, see section [18.1](#).

## **3.2 Rationale for the trial**

The currently available treatment modalities for T2D are still not satisfactory and there is a significant proportion of patients not reaching the treatment targets<sup>6</sup>.

The aim for the present trial is to compare the effect of semaglutide versus canagliflozin, in subjects with T2D inadequately controlled with metformin, in terms of glycaemic control, weight

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management and other efficacy parameters. This trial is also designed to compare safety profile, tolerability and patient satisfaction.

In order to further investigate the effects of semaglutide vs canagliflozin on body weight, a sub-study on body composition has been implemented in this trial, which will allow collection of information on changes in body fat and lean mass.

## 4 Objective(s) and endpoint(s)

### 4.1 Objective(s)

#### Primary objective

To compare the effect of once-weekly dosing of subcutaneous semaglutide (1.0 mg) versus once-daily dosing of oral canagliflozin (300 mg) on glycaemic control in subjects with T2D on a background treatment of metformin.

#### Secondary objective

To compare the effect of semaglutide s.c. 1.0 mg once-weekly versus canagliflozin 300 mg once-daily after 52 weeks of treatment in subjects with T2D with regards to:

- Weight management
- Other parameters of effect, safety and Patient Reported Outcomes (PRO)

### 4.2 Endpoint(s)

#### 4.2.1 Primary endpoint

- Change from baseline to week 52 in HbA<sub>1c</sub>

#### 4.2.2 Secondary endpoints

##### 4.2.2.1 Confirmatory secondary endpoints

##### Change from baseline to week 52 in

- body weight (kg)

In a sub-set of subjects assessed through dual X-ray absorptiometry (DXA):

- Total fat mass (kg)

##### 4.2.2.2 Supportive secondary efficacy endpoints

##### Change from baseline to week 52 in:

- Fasting Plasma Glucose (FPG)\*
- Self-Measured Plasma Glucose (SMPG), 7-point profile:
  - Mean 7-point profile
  - Mean post prandial increment (over all meals)
- Fasting blood lipids (total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglycerides)
- Systolic and diastolic blood pressure\*
- Body Mass Index (BMI) and waist circumference
- Body weight (%)
- Scores for selected patient reported outcomes:

- SF-36v2<sup>TM</sup> Short Form health survey: Total scores (physical component and mental component) and scores from the 8 domains
- Diabetes Treatment Satisfaction Questionnaire (DTSQ)\*: Treatment satisfaction score (sum of 6 of 8 items) and the 8 items separately
- Control of Eating Questionnaire (CoEQ): Scores from the 4 domains and scores from 19 individual items

In a sub-set of subjects, assessed through DXA, change from baseline to week 52 in:

- Total fat mass (%)
- Total lean mass (kg)
- Total lean mass (%)
- Visceral fat mass (kg)<sup>a</sup>
- Visceral fat mass (%)<sup>a</sup>
- Ratio between total fat mass and total lean mass

<sup>a</sup>analyses marked with an 'a' will be performed based on specific DXA equipment and software availability.

#### **Subjects who after 52 weeks treatment achieve (yes/no):**

- HbA<sub>1c</sub> <7.0% (53 mmol/mol), American Diabetes Association (ADA) target
- HbA<sub>1c</sub> ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists (AACE) target\*
- Weight loss ≥3%
- Weight loss ≥5%
- Weight loss ≥10%
- HbA<sub>1c</sub> <7.0% (53 mmol/mol) without severe or blood glucose confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA<sub>1c</sub> reduction ≥1%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥3%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥5%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥10%

#### **4.2.2.3 Supportive secondary safety endpoints**

- Number of treatment emergent adverse events (TEAEs)
- Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes
- Treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemia episodes (yes/no)

**Change from baseline to week 52 in:**

- Haematology
- Biochemistry
- Calcitonin
- Pulse
- Electrocardiogram (ECG) category
- Physical examination category
- Eye examination category

Key supportive secondary endpoints prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT) are marked with an asterisk (\*).

## 5 Trial design

### 5.1 Type of trial

This is a 52-week, confirmatory, randomised, double-blind, double dummy, active-controlled, multicentre, multinational, two-arm, parallel-group trial.

Subjects with T2D inadequately controlled on metformin alone, will after approximately 2 weeks screening period, be randomised in a 1:1 manner to receive either semaglutide 1.0 mg once-weekly and canagliflozin placebo once-daily, or canagliflozin 300 mg once-daily and semaglutide placebo once-weekly after a dose escalation phase of 8 weeks, see [Figure 5-1](#).

Subjects continue participation in the trial regardless of premature discontinuation of trial product or the initiation of rescue medication.

After the treatment period of approximately 52 weeks in total, all subjects enter a follow-up period of 5 weeks which ends by a follow-up visit. Total trial duration for the individual subjects is approximately 59 weeks.

The randomisation will be stratified according to the participation in the sub-study (yes or no) in order to ensure balanced treatment allocation within the sub-study.

The trial design is summarised schematically in [Figure 5-1](#).

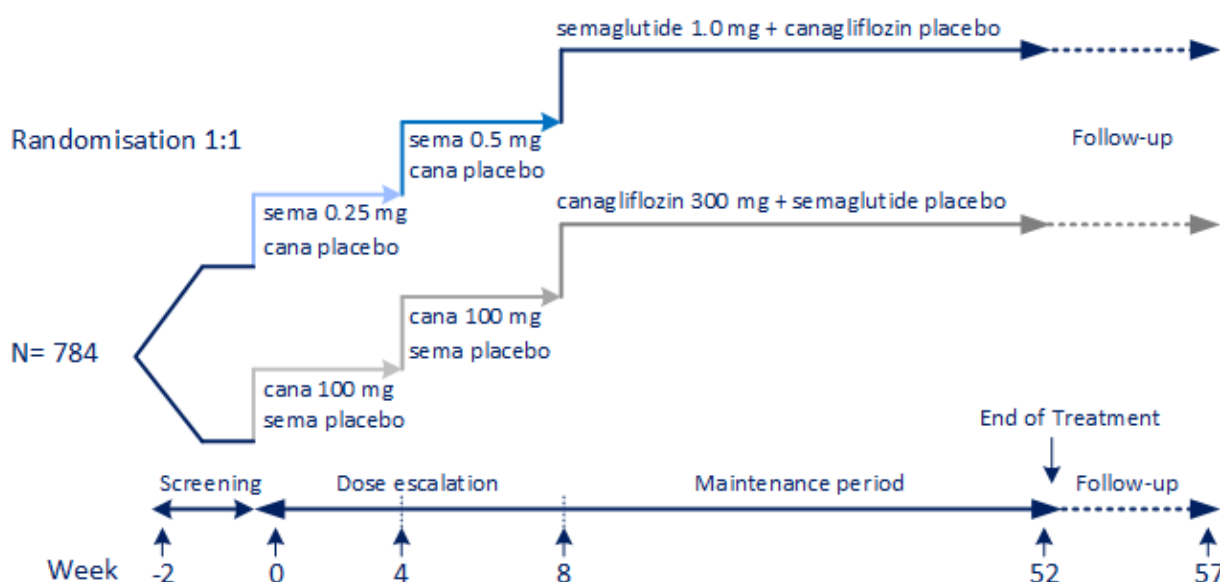


Figure 5-1 Trial design

## 5.2 Rationale for trial design

This trial has been designed as a double-blind, two-arm, parallel-group trial to compare the effect of semaglutide s.c. 1.0 mg once-weekly versus canagliflozin 300 mg once-daily, as add-on to metformin, in terms of glycaemic control, weight management and other effect parameters. Furthermore, the trial is designed to address and compare safety, tolerability, patient well-being and treatment satisfaction. Body composition will be measured using dual energy x-ray absorptiometry (DXA) in a subset of 174 subjects (87 subjects per treatment arm) at V1 and V10 or V10A.

Semaglutide is administered as s.c. injections and canagliflozin as oral tablets. In order to fulfil blinding of the trial, a double-dummy design has been implemented. Accordingly, all subjects randomised to semaglutide s.c. will also receive canagliflozin placebo tablets, while subjects randomised to canagliflozin will also receive semaglutide placebo s.c. injections.

The treatment duration is 52 weeks, considered adequate for assessment of effect, safety, tolerability and patient satisfaction.

The follow-up period is 5 weeks to allow for wash-out of semaglutide.

## 5.3 Treatment of subjects

### Semaglutide treatment arm

Treatment with semaglutide, once-weekly must follow a fixed dose escalation. The maintenance dose of semaglutide 1.0 mg is reached after 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg. During the final maintenance period (V4-V10), doses must not be changed. In addition, all subjects randomised to semaglutide will receive canagliflozin placebo once-daily.

### Canagliflozin treatment arm

Treatment with canagliflozin, once-daily must follow a fixed dose escalation. The maintenance dose of canagliflozin 300 mg is reached after 56 doses (8 weeks) of 100 mg. After the maintenance dose of 300 mg is reached the dose must not be changed during the course of the trial unless the eGFR falls  $<60 \text{ mL/min/1.73 m}^2$ , see below. In addition, all subjects randomised to canagliflozin will receive semaglutide placebo once-weekly.

Treatment with canagliflozin must be in compliance with current local prescribing information. Canagliflozin should be taken orally once a day, preferably before the first meal of the day. Tablets should be swallowed whole. Treatment with canagliflozin or canagliflozin placebo should be temporarily stopped in subjects who are hospitalized for major surgical procedures or acute serious medical illnesses. In subjects whose eGFR falls persistently  $<60 \text{ mL/min/1.73 m}^2$ , the dose of canagliflozin or canagliflozin placebo should be reduced to 100 mg once-daily. The dose can be re-escalated to 300 mg once-daily in case the renal function improves ( $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$ ) during the trial. If the eGFR falls  $<45 \text{ mL/min/1.73 m}^2$ , treatment with all trial products should be discontinued (see section [6.6](#))<sup>1</sup>.



### **5.3.1 Background medication**

The only allowed diabetes background medication is metformin. After signing the informed consent, subjects must continue pre-trial dose ( $\geq 1500$  mg or maximum tolerated dose as documented in the subject medical record and in accordance with current local label) of metformin throughout the entire treatment period, at the same dose level as given at trial entrance and with the same frequency, unless rescue criteria (see section [6.5](#)) are met.

#### **Metformin**

Metformin is considered non-investigational medicinal product (NIMP) and will not be provided by Novo Nordisk, except if required by local regulations. Metformin should be used in accordance with standard of care in the individual country at the discretion of the investigator and in compliance to the current local label.

### **5.4 Injection site**

Semaglutide (and semaglutide placebo) is administered subcutaneously by injections in the thigh, abdomen or upper arm, at any time of the day irrespective of meals. Injections should be administered on the same day of the week during the trial. Injections should not be administered intravenously or intramuscularly.

### **5.5 Missed dose**

If a semaglutide dose is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (48 hours) away. If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the subject should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing time of the week.

If a canagliflozin dose is missed it should be taken as soon as the subject remembers; however, a double dose should not be taken on the same day.

### **5.6 Treatment after discontinuation of trial product**

When discontinuing trial products, either at the scheduled end of treatment visit or if trial product is discontinued prematurely, the subject should be switched to a suitable marketed product at the discretion of the investigator, while taking into consideration the long half-life of semaglutide.

*For Brazil only: At the end of the trial, all participant subjects should be assured the access to the best proved prophylactic, diagnostic and therapeutic methods identified during the trial.*

## **5.7 Rationale for treatment**

Semaglutide has been developed for s.c. administration. The dose of 1.0 mg once-weekly has been chosen based on careful evaluation to strike a satisfactory balance of efficacy and safety that would satisfy the majority of subjects. Hence, the duration and the dose of the randomised treatments are considered adequate for obtaining meaningful information on effect and safety in accordance with the trial objectives. Subjects will be enrolled for a treatment period of 52 weeks in order to enable evaluation of the full effect and durability of the primary and secondary endpoints as well as reasonable safety assessment.

For semaglutide, the three dose levels (0.25, 0.5 and 1.0 mg), have been chosen based on data from the phase 2 dose-finding trial. This regimen has shown the optimal benefit-risk profile for further development for treatment of T2D in the SUSTAIN programme<sup>25</sup>.

Canagliflozin has been chosen as active comparator since it is an established OAD within the drug class of SGLT-2 inhibitors and treatment will be initiated with 100 mg in accordance with the current approved EU-PI<sup>32</sup>.

Both s.c. semaglutide and oral canagliflozin will be dose escalated to their highest respective maintenance doses to investigate and compare the maximum efficacy of the two medications when added to metformin.

The duration of randomised treatments is considered adequate to collect sufficient data on effect and safety in accordance with the trial objectives.

## 6 Trial population

### 6.1 Number of subjects

Number of subjects planned to be screened (meaning the number of subjects providing informed consent):	1307
Number of subjects planned to be randomised in a 1:1 manner:	784
Number of subjects planned to be randomised in sub-study on body composition:	174
Number of subjects planned to complete the trial on randomised trial product without rescue medication.	549

*For Mexico only: Approximately 83 subjects are planned to be screened and 50 subject are planned to be randomised in Mexico.*

### 6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered “yes”.

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age above or equal to 18 years at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus (T2D).
4. HbA<sub>1c</sub> of 7.0-10.5% (53-91 mmol/mol, both inclusive).
5. Stable daily dose of metformin ( $\geq 1500$  mg or maximum tolerated dose as documented in the subject medical record and in compliance with current local label) for at least 90 days prior to the day of screening.

### 6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered “no”.

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.

*For Brazil Only: Participation in other trials within one year prior to screening visit (Visit 1) unless there is a direct benefit to the research subject at the investigator's discretion.*

3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

*For Brazil only: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.*

*For EU countries only:*

*The following contraceptive measures are considered adequate:*

- *Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)*
- *Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)*
- *Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)*
- *Bilateral tubal occlusion*
- *Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository). (Not applicable for Sweden and the UK).*
- *Vasectomised partner (where partner is sole partner of subject) and that the vasectomised partner has received medical assessment of the surgical success.*
- *True sexual abstinence. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.*

4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days prior to the day of screening.
5. Any disorder which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
6. Subjects with ALT >2.5 x upper normal limit (UNL).
7. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family is defined as a first degree relative.
8. History or presence of pancreatitis (acute or chronic).
9. History of diabetic ketoacidosis (DKA).
10. Any of the following: myocardial infarction (MI), stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
11. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
12. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
13. Renal impairment measured as eGFR <60 ml/min/1.73 m<sup>2</sup> as defined by Kidney Disease Improving global outcomes (KDIGO 2012)<sup>1</sup> classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening. .

14. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed.
15. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.
16. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.
17. Medical history of diabetes-related lower limb amputations or signs of critical lower limb ischemia, (e.g. skin ulcer, osteomyelitis, or gangrene) within the last 26 weeks prior to screening.

#### **6.4 Randomisation criteria (only applicable for the DXA scan sub-population)**

To be randomised, all randomisation criteria must be answered “yes”.

1. The quality evaluation of the baseline DXA scan needs to be performed and found acceptable by the imaging laboratory prior to randomisation.

#### **6.5 Rescue criteria**

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification and the conclusion of the consideration to be documented in the medical records. If any of the FPG values (see section [8.5.1](#)) (including protocol scheduled fasting SMPG, see section [8.6.1](#)) exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified, a confirmatory FPG (at central laboratory) should be obtained by calling the subject for a re-test.

- 13.3 mmol/L (240 mg/dL) from week 8 to end of week 13
- 11.1 mmol/L (200 mg/dL) from week 14 to end of treatment

In addition, subject should be offered rescue medication if:

- HbA<sub>1c</sub> (at central laboratory) >8.5 % (69.4 mmol/mol) from week 26 to end of treatment.

If the confirmatory FPG also exceeds the value described above, the subject should be offered rescue medication (i.e. intensification of anti-diabetic background medication and/or initiation of new anti-diabetic medication).

It is important for trial integrity that only subjects actually needing treatment intensification (as defined above) are started on rescue medication. Subjects that are started on rescue medication should continue to follow the protocol-specified visit schedule. Rescue medication should be prescribed at the investigator's discretion as add-on to randomised treatment and according to

American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines<sup>33, 34</sup> (excluding GLP-1RAs, DPP-4 inhibitors, amylin analogues and SGLT-2).

Rescue medication and any changes hereto should be captured on the concomitant medication form in the electronic case report form (eCRF), see Section [13](#). Rescue medication is considered to be NIMP and will not be provided by Novo Nordisk, unless required by the country's Health Authority or IEC/IRB.

## **6.6 Criteria for premature discontinuation of trial product**

All efforts should be made to keep the subject on trial product. However, the subject might be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

If so, all efforts must be made to ensure the subjects attend and complete all scheduled visit procedures. Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial will be considered as withdrawn from the trial (see Section [6.7](#)).

The subject must be prematurely discontinued from trial product, if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Safety concern related to trial product or unacceptable intolerability at the discretion of the investigator
3. Pregnancy\*
4. Intention of becoming pregnant\*
5. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
6. If the eGFR falls persistently  $<45 \text{ mL/min/1.73m}^2$ , treatment with any trial product should be discontinued (see section [5.3](#))
7. Calcitonin  $\geq 100 \text{ ng/L}$  (see [appendix A](#))
8. Lower limb amputations or signs of critical limb ischemia, (e.g. skin ulcer, osteomyelitis, or gangrene)

\*No DXA scans can be performed on these subjects.

See Section [8.1.8](#) for procedures to be performed for subjects discontinuing trial product prematurely.

The primary reason for discontinuation of trial product must be specified in the eCRF.

If a criterion for premature discontinuation of trial product is met, trial product should not be re-initiated but subjects should continue with protocol-specified visit schedule.

## 6.7 Withdrawal from trial

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected. Only subjects who withdraw consent should be considered as withdrawn from trial.

See Section [8.1.9](#) for procedures to be performed for subjects withdrawing consent.

*For Mexico only: Should the subject his/her family members parents or legal representative decide to withdraw the consent for participation in the trial, the subject will be entitled to receive appropriate, free of charge medical care and/or trial drug during the follow up period of the protocol when it will be established with certainty that no untoward medical consequences of the subject's participation in the research occurred.*

## 6.8 Subject replacement

Subjects who discontinue trial product prematurely will not be replaced.

## 6.9 Rationale for trial population

The trial population will include subjects with T2D treated with stable doses of metformin for at least 90 days prior to screening as changes in the background medication shortly before trial participation may potentially impact data interpretation. The HbA<sub>1c</sub> limits of 7.0-10.5% (53-91 mmol/mol) have been chosen to include subjects needing intensification of their anti-diabetic medication. FPG and HbA<sub>1c</sub> will be monitored throughout the trial and rescue medication should be initiated in subjects with persistent, unacceptable hyperglycaemia. No BMI or blood pressure restrictions are applied. Subjects with liver test abnormalities (ALT >2.5 x UNL) are excluded to avoid potential confounding of liver safety assessments. In addition, subjects with mild, moderate, severe or end-stage renal impairment are excluded due to restrictions in the labels of canagliflozin and metformin. As SGLT-2 inhibitors have been associated with diabetic ketoacidosis, subjects with a history of diabetic ketoacidosis are also excluded from this trial. Overall, the eligibility criteria will allow for enrolment of a relatively broad trial population resembling the target population in common practice while taking relevant safety precautions.

## 7 Milestones

Planned duration of recruitment period 28 weeks.

Planned date for FPFV: 15-Mar-2017

Planned date for LPLV: 21-Nov-2018

End of trial (P11) is defined as LPLV.

### **Recruitment:**

The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

### **Trial registration:**

Information of the trial will be disclosed at [clinicaltrials.gov](http://clinicaltrials.gov) and [novonordisk-trials.com](http://novonordisk-trials.com). According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure<sup>35</sup>, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)<sup>36</sup>, the Food and Drug Administration Amendment Act (FDAAA)<sup>37</sup>, European Commission Requirements<sup>38, 39</sup> and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.



## 8 Methods and assessments

### 8.1 Visit procedures

The following sections describe the assessments and procedures. These are also included in the flow chart (see Section [2](#)) as well as visit numbers, timing of site and phone visits and windows during the trial period.

Informed consent must be obtained before any trial related activity, see Section [18.3](#).

For each Dispensing visit; interact with IWRS to obtain allocation of trial products, confirm dispensing of allocated trial products and, except for the randomisation visit, confirm trial products returned unused or lost.

A treatment completion session must be performed in the IWRS after completion of V10.

#### 8.1.1 Investigator site log

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log.

In addition, the investigator must keep a log of staff and a delegation of task(s) list at the trial site. Investigator must sign the log of staff and the delegation of task(s) at the trial site prior to the delegation of tasks.

#### 8.1.2 Screening, Visit 1

At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

#### 8.1.3 Screening failures

For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious adverse events (SAEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events must be carried out according to Section [12](#).

A screening failure session must be made in the IWRS and the screening failure form completed in the eCRF. The case book must be signed.

#### **8.1.4 Re-screening**

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria or randomisation criteria; this includes re-sampling if the subject has failed one if the inclusion or exclusion criteria related to laboratory parameters.

#### **8.1.5 Fasting visits**

The subjects should attend site visits in a fasting state (see section [2](#) for details). Fasting is defined as having consumed only water within the last 6 hours prior to the visit.

If the subject does not attend the visit in a fasting state, the subject should be asked to attend a re-scheduled visit within the visit window to have the fasting assessments performed.

Glucose lowering agents and trial product should not be taken until after blood sampling has been performed but other prescribed medication should be taken according to prescription.

#### **8.1.6 Unscheduled visits**

Unscheduled visits can be performed at the investigators discretion if an AE requires additional follow-up or if required by the Novo Nordisk department responsible for safety. Unscheduled visits can take place at any time during the trial from screening until the last visit in the trial. Further, unscheduled visits for re-sampling can take place if laboratory samples are lost or damaged before arriving at the analysing laboratory. This re-sampling will be at the discretion of the Novo Nordisk medically responsible person in collaboration with the investigator.

All assessments performed at any time during the trial can be performed during unscheduled visits with the exception of DXA body composition scan (only permitted if required due to DXA technical reasons), waist circumference and ePROs.

Visits/contacts to the site not related to the trial do not need to be reported as an unscheduled visit. Contacts for re-dispensing of trial drug as replacement for lost or damaged trial drug do not need to be recorded as unscheduled visits but need to be recorded in the IV/WRS.

#### **8.1.7 Phone contacts**

The phone contacts should be conducted as outlined in the flow chart (see Section [2](#)).

At V2, and V3 the investigator should instruct the subject how to dose escalate semaglutide/semaglutide placebo up to 1.0 mg once-weekly and also how to dose escalate canagliflozin up to 300 mg daily. At the planned phone contact (P5), the investigator should follow-up on any symptoms associated with diabetic ketoacidosis (DKA), any AEs as well as compliance and potential technical issues in regards to the dose escalation.

At the phone contacts at P11 and P11A occurring at least 5 weeks after V10 or V10A the investigator should follow up on any new concomitant medication, hypoglycaemic episodes or any AEs.

### **8.1.8 Premature discontinuation of trial product**

If a subject prematurely discontinues trial product, the investigator must undertake procedures described for V10A as soon as possible (preferably the same day), which are similar to those at V10. P11A should be scheduled at least 5 weeks after the last date on trial product.

If premature discontinuation of trial product is decided during a scheduled visit, the visit will be converted into a V10A and trial procedures must be performed accordingly.

Subjects should continue with the originally scheduled site contacts after P11A and up to and including P11. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after P11A. However, all attempts should be made to ensure that V10 is performed as a site visit and includes all planned assessments.

In summary, subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule, missing assessments or trial product discontinuation for any reason. Only subjects who decline any further contact with the site in relation to the trial should be considered as withdrawn from the trial (for withdrawal procedures see Section [8.1.9](#)).

The primary reason for premature discontinuation of trial product must be specified in the end-of-treatment form in the eCRF, and final drug accountability must be made. A treatment discontinuation session must be performed in the IWRS at V10A (see Section [10](#)).

### **8.1.9 Withdrawal from trial**

If a subject withdraws consent, the investigator must aim to undertake procedures similar to those for V10A (End of treatment) as soon as possible. If a subject has already prematurely discontinued from trial product and previously attended visit V10A and visit P11A, no further visits should be attended.

For withdrawn subjects the end-of-trial form and end-of-treatment form must be completed, including the primary reason for premature discontinuation of trial product, and final drug accountability must be performed even if the subject is not able to come to the trial site.

A treatment discontinuation session must be made in the IWRS, however if a subject has already prematurely discontinued from trial product and a treatment discontinuation session in IWRS has been done, no IWRS session should be completed. The case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing consent, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

Where the reasons are obtained, the primary reason for withdrawing consent must be specified in the end-of-trial form in the eCRF.

#### **8.1.10 Investigator assessment**

Review of diaries, ePROs, laboratory reports, ECGs, dilated funduscopy/fundus photography, physical examinations etc. must be documented with the investigator's or delegate's dated signature either on the front page of the documents and/or in the subjects medical record. The signed documents must be retained at the trial site as source documentation.

For ECGs, physical examinations and dilated funduscopy/fundus photography the evaluations must follow the categories:

- Normal
- Abnormal
  - Was the result clinically significant (No/Yes)

The evaluation should be based on the investigator's or delegate's judgement.

For laboratory report values outside the reference range, the investigator must specify whether the value is clinically significant or clinically non-significant. All laboratory printouts must be signed and dated by the investigator on the day of evaluation. The signed laboratory report is retained at the site as source documentation.

In case of abnormal clinical significant findings found as a result of screening procedures conducted at visit 1 or assessments revealing baseline conditions at visit 2, the investigator must state a comment in the subject's medical record and record this in the concomitant illness form in the eCRF. At subsequent visits, any clinically significant changes or new clinically significant findings must be reported as an AE according to section [12](#).

Investigator or trial site staff must review the diary to ensure that AEs, including overall changes in health and concomitant medication, are reported.

If clarification of entries or discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

### **8.2 Subject related information/assessments**

#### **8.2.1 Demography**

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

### 8.2.2 Diabetes history and diabetes complications

Diabetes history and diabetes complications will be recorded at screening and consists of:

- Date of diagnosis of type 2 diabetes
- Information regarding diabetes complications including date of onset
  - Diabetic retinopathy
  - Diabetic neuropathy
  - Diabetic nephropathy
  - Macroangiopathy (including peripheral vascular disease)

### 8.2.3 Hypoglycaemia unawareness

Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8<sup>40</sup>.

The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" The subject can answer never, rarely, sometimes, often or always. Subjects answering 'never, rarely or sometimes' are considered as having impaired awareness of hypoglycaemia.

### 8.2.4 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial as described in section [8.1.10](#).

**Medical history** is a medical event that the subject has experienced in the past. Only relevant medical history as judged by the investigator should be reported.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

It must be possible to verify the subject's medical history in source documents such as subject's medical record. If a subject is not from the investigator's own practice; the investigator must make reasonable effort to obtain a copy of subject's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

### 8.2.5 Concomitant medication

A **concomitant medication** is any medication, other than the trial product(s) which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at the first visit (screening visit). Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes:

- trade name or generic name,
- indication, start date (only start year is applicable if more than one year) and stop date or continuation.
- total daily dose (only applicable for anti-diabetic medication)

If a change is due to an AE, then this must be reported according to Section [12](#). If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

### **8.2.6 Childbearing potential**

It must be recorded in the eCRF whether female subjects are of childbearing potential.

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section [8.5.2](#). Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 5 weeks after end of treatment.

Female of non-childbearing potential is defined as:

- Female who has undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation or are postmenopausal (e.g. women above the age of 50, who have been without menstrual period for at least 1 year).
- Other medical reasons preventing childbearing potential

For Argentina only: Birth control methods will be reimbursed by Novo Nordisk Pharma Argentina S.A.

For Brazil only: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.

For EU countries only:

*The following contraceptive measures are considered adequate:*

- *Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)*
- *Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)*
- *Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)*
- *Bilateral tubal occlusion*
- *Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository). (Not applicable for the Sweden and UK).*
- *Vasectomised partner (where partner is sole partner of subject) and that the vasectomised partner has received medical assessment of the surgical success.*
- *True sexual abstinence. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.*

### **8.2.7 Tobacco use**

Details of tobacco use must be recorded at the screening visit. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked.

Smoking status:

- Never smoked
- Previous smoker, smoking stop date
- Current smoker

## **8.3 Efficacy assessments**

### **8.3.1 Height, body weight and BMI**

Height is measured without shoes in cm or inches and recorded to nearest ½ cm or ¼ inch.

Body weight should be measured and recorded in the eCRF in kilogram or pound (kg or lb), with one decimal, without shoes and only wearing light clothing.

BMI will be calculated in the eCRF every time the weight is measured using the equation:

$$\text{BMI} = \text{body weight (kg)} / (\text{height (m)} \times \text{height (m)}) \text{ or } [\text{kg/m}^2 = \text{lb/in}^2 \times 703]$$

### **8.3.2 Waist circumference**

The waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest.

The measurement of waist circumference should be performed and recorded in the eCRF. The

waist circumference will be measured using a non-stretchable measuring tape. It should be recorded to the nearest ½ cm or ¼ inch using the same measuring tape throughout the trial.

The waist circumference should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The tape should touch the skin but not compress soft tissue. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

### **8.3.3 Systolic and diastolic blood pressure**

Systolic and diastolic blood pressure should be measured in a sitting position after the subject has been resting for at least 5 minutes and by using standard clinical practice at the trial site.

### **8.3.4 Self-measured plasma glucose (SMPG)**

At the screening visit, subjects will be provided with a blood glucose meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use. The blood glucose meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

Only the blood glucose meter provided by Novo Nordisk should be used for the measurements required in the protocol.

Subjects should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

Occasional review by the investigator of the values stored in the memory of the blood glucose meter and correct reporting of these in the diary is advised in order to ensure adequacy of the data reported in the trial database.

### **8.3.5 7-point profile**

The subject will be asked to perform a 7-point SMPG profile, preferably within one week prior to site visit according to the flow chart, on days where the subject does not anticipate unusual strenuous exercise.

Time points, including date and time, for the 7-point profile:

- before breakfast
- 90 min after start of breakfast



- before lunch
- 90 min after start of lunch
- before dinner
- 90 min after start of dinner
- at bed time

### 8.3.6 DXA scan (sub-population only)

Body composition will be measured using dual energy x-ray absorptiometry (DXA) whole body scans. These scans will be performed in a sub-set of 174 randomised subjects (approximately 87 subjects per treatment arm). The overall process of image acquisition, transfer, central analysis, reporting of results and archiving is described in an **Imaging Charter** prepared by the laboratory. The baseline DXA scan will be performed at screening (V1+5 days), this to allow the imaging laboratory to confirm the quality of the scan, prior randomisation. It is recommended the site confirms patient eligibility prior performing the DXA scans. At the end of treatment visit (V10 or V10A), the scans must be performed  $\pm 5$  calendar days.

The quality of the baseline DXA scan obtained at V1 must be confirmed by the imaging laboratory before the subject can be randomised. The quality of the DXA scans will be evaluated by the imaging laboratory designated by Novo Nordisk for reading in a blinded manner. If a subject withdraws prematurely from the trial, an end of trial DXA scan should preferably be performed.

Process for image acquisition is outlined in an **Image acquisition guideline (IAG)**. Besides the two scans per subject described in this protocol a limited number of repeat scans might be acquired if required due to technical reasons. Repeated scans should not be performed if the subject has prematurely discontinued trial medication due to pregnancy or intention of becoming pregnant.

A cross calibration using cross calibration phantom will be performed at least once at each site prior to the database lock (DBL) of the trial.

Each trial site participating in the sub-study will receive an **imaging manual** prepared and distributed by the imaging laboratory which will include machine specific instructions for acquiring DXA scans. The manual will serve as reference tool for use during the trial and when training technologists. DXA technologist training will occur at the start of the trial and at any time deemed necessary to assure proper scan acquisition.

Following DXA scan acquisition each trial site will be responsible for transferring each DXA scan to the imaging laboratory for quality review and analysis. DXA analysis data will include:

- Total fat mass (kg)
- Total fat mass (%)
- Total lean mass (kg)

- Total lean mass (%)
- Visceral fat mass (kg)\*
- Visceral fat mass (%)\*
- Ratio between total fat mass and total lean mass

\*analyses marked with an asterisk will be performed based on specific DXA equipment and software availability.

DXA analysis data will be transferred from the imaging laboratory to Novo Nordisk immediately prior to the DBL of the trial. The investigators will receive the results from the analysis only after LPLV in order to avoid un-blinding.

## **8.4 Safety assessments**

### **8.4.1 Physical examination**

A physical examination must be performed at V1, V8 and V10/V10A (or as specified below) and include the following:

- General appearance
- Skin
- Thyroid gland
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Central and peripheral nervous system
- Lymph node palpation
- Legs and feet\*

\*Physical examination of legs and feet must be performed at every site visit.

### **8.4.2 Pulse**

Pulse (beats per minute) should be recorded at the site of visits after resting for 5 minutes in a sitting position.

### **8.4.3 Electrocardiogram – 12 lead**

A 12-lead ECG must be performed and interpreted locally by the investigator as described in section [8.1.10](#)

It is allowed to perform the baseline ECG between the screening visit and the randomisation visit. The result should be available prior to randomisation. An ECG performed for any reason unrelated to this trial within 7 days prior to the screening visit is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime.

If the ECG was performed as part of a routine clinical practice on/before the date when the subject has signed the informed consent, it must be documented in the medical records that the reason for performing the procedure is not related to this trial.

#### **8.4.4 Eye examination**

The eye examination will be performed as per flowchart (see section [2](#)).

It is allowed to perform the baseline fundus photography or dilated fundoscopy between the screening visit and the randomisation visit. Results of the baseline fundus photography or dilated fundoscopy must be available and evaluated by the investigator before randomisation. If the subject had a fundus photography or dilated fundoscopy performed within 90 days prior to randomisation, the investigator may base their evaluation upon the results of that examination. However, the examination must be repeated before randomisation if the subject experienced worsening of visual function since the last examination. If the subject did not have a fundus photography or dilated fundoscopy performed within 90 days prior to randomisation, such examination must be performed by the investigator or other qualified health care professional prior to randomisation. If the applicable fundus photography or dilated fundoscopy was performed before the subject signed the informed consent form, it must be documented in the medical records that the reason for performing the examination was not related to this trial.

In addition, dilated fundoscopy/fundus photography must be performed at V10. In the case of premature discontinuation, the assessments must be performed both at V10A and at V10. The assessments at V10A and V10 can be performed in the period between V10A and P11A, and between V10 and P11, respectively but the results should be available no later than at P11A and P11, respectively.

The investigator should indicate whether the outcome of the eye examination was normal or abnormal, and, if abnormal, indicate whether clinically significant. Relevant findings as a result of this screening procedure must be recorded as concomitant illness/medical history in accordance with section [8.2.4](#).

#### **8.4.5 Adverse events**

AEs must be reported at each visit in accordance with the procedures outlined in Section [12](#).

##### **8.4.5.1 Medication error**

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form:

- Trial product(s) involved
- Classification of medication error

- Whether the subject experienced any hypoglycaemic episode and/or adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section [12.1.4](#).

#### **8.4.5.2 Adverse events requiring additional data collection**

For the following AEs additional data collection is required and specific event forms must be completed in addition to the AE form:

- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or transient ischaemic attack)
- Heart failure
- Hypersensitivity reaction
- Neoplasm (excluding thyroid neoplasm)
- Pancreatitis
- Renal Event
- Thyroid disease (including thyroid neoplasm)
- Hepatic event
- Diabetic retinopathy
- Laboratory outlier

See [appendix B](#) for details about the additional information to report.

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section [12](#).

#### **8.4.6 Hypoglycaemic episodes**

Plasma glucose should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose values:

- $\leq 3.9$  mmol/L (70 mg/dL) or
- $> 3.9$  mmol/L (70 mg/dL) occurring in conjunction with hypoglycaemic symptoms

should be reported in the diary according to the instructions below in section [8.6.1](#) throughout the trial from visit 1 to visit 10/10A. For the follow-up visit (P11/P11A) the hypoglycaemic episode(s) should be documented in the subject's medical record.

All information must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from visit 1 to visit 11/11A.

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is  $>3.9$  mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines<sup>41</sup>.

An SMPG value  $\leq 3.9$  mmol/L (70 mg/dL) or hypoglycaemic symptoms will be recorded in the diary in the hypoglycaemic episode form by the subject. Repeated SMPG measurements and/or symptoms, will by default be considered as one hypoglycaemic episode until a succeeding SMPG value is  $>3.9$  mmol/dL (70 mg/dL) and/or symptoms have been resolved. One hypoglycaemic episode form is to cover these measurement and/or symptoms.

In case of several low SMPG values within the hypoglycaemic episode, the lowest value is the one that will be reported as the SMPG value for the hypoglycaemic episode but the start time of the episode will remain as the time for the first SMPG value and/or symptom.

The record should include the following information:

- Start date and time of the hypoglycaemic episode
- Stop date and time of the hypoglycaemic episode (stop time is the first time plasma glucose value is  $>3.9$  mmol/L (70 mg/dL) and/or symptoms have been resolved).
- If a stop date and time is not reported, a hypoglycaemic episode will cover a period of 60 minutes.
- The PG level before treating the episode (if available) and any follow up measurements.
- The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode, the remaining values will be kept as source data in the diary.
- Whether the episode was symptomatic (Yes/No)
- A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode.
- Whether the subject was able to treat him/herself
- If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported, reflecting the most severe degree of hypoglycaemia.
- Date-and time of last trial product administration and other anti-diabetic medications prior to the episode
- Date and time of last main meal (not including snacks) prior to the episode
- Whether the episode occurred in relation to physical activity
- Change in any concomitant illness
- Any sign of fever and/or other acute disease
- Whether the subject was asleep when the episode occurred
  - If yes, whether the symptoms of the episode woke up the subject

The answer to the question: "Was the subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but

neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration<sup>41</sup>.

Oral carbohydrates must not be given if the subject is unconscious.

If the question "Was the subject able to treat him/herself?" is answered "No", the following information should be recorded by the subject:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of dose of antidiabetic medication, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms (layman term used in the diary is specified in brackets if different from the protocol term)?<sup>41</sup>
  - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
  - General malaise: headache or malaise (feeling discomfort/unease)
- Other symptoms

The investigator must review the diary for low SMPG values not reported as hypoglycaemic episodes. The subject must be questioned whether any of the low values were severe, i.e. whether the subject was able to self-treat or not. If the subject was not able to self-treat, it has to be reported as a severe hypoglycaemic episode.

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data<sup>42, 43</sup>.

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low SMPG values not reported as hypoglycaemic episodes.

If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must also be filled in, see section [12](#).

## **8.5 Laboratory assessments**

The laboratory assessments will be performed by a central laboratory. If collected, anti-semaglutide IgE antibody samples will be analysed by Novo Nordisk (for further details see Section [18.1.1](#)). The central laboratory may utilise sub-contractors.

In the events described in section [8.4.5.2](#), a local laboratory must be used.

Descriptions of assay methods, laboratory supplies and procedures for collecting, handling, storage and shipping of samples, will be described in the laboratory manual provided by the central laboratory.

*For Mexico only: Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling, transportation and storage of biological samples and information regarding who will perform the assessments, will be described in a trial specific laboratory manual, provided by the central laboratory (for central laboratory details, see [attachment 1](#)).*

Laboratory samples not drawn on the day of the actual visit should preferably be drawn on another day within the visit window stated in the flow chart. For some of the samples drawn during the trial, subjects will be asked to attend the relevant site visits fasting (see section [8.1.5](#)).

Laboratory results will be sent by the central laboratory to the investigator on an on-going basis and the investigator must review all laboratory results for signs of concomitant illness and AEs and report these according to this protocol (see section [12](#)).

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to Section [8.2.4](#) and Section [12](#).

*For Brazil only: All laboratory results will be communicated to the investigators.*

Only laboratory samples specified in the protocol must be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.

All laboratory samples will be destroyed at the latest at the completion of the clinical trial report or according to local regulations.

*For Brazil only: Biological samples from Brazil will be destroyed at the end of the trial.*

### **8.5.1 Laboratory assessments for efficacy**

Blood samples will be drawn according to flow chart and analysed at the central laboratory to determine levels of the following efficacy laboratory parameters:

- Glucose metabolism:
- HbA<sub>1c</sub>
- FPG
- Lipids (all fasting):
  - Total cholesterol
  - LDL cholesterol
  - HDL cholesterol
  - Triglycerides

#### **Fasting plasma glucose**

FPG is measured at central laboratory in order to evaluate glycaemic control. The subject must attend these visits fasting (see Section [8.1.5](#)).

A central FPG result obtained at the central laboratory of  $\leq 3.9$  mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see Section [12.1.1](#)).

### **8.5.2 Laboratory assessments for safety**

Blood samples will be drawn and analysed at the central laboratory to determine levels of the following laboratory parameters:

Biochemistry:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Albumin, bilirubin (total)
- Alkaline phosphatase,
- Potassium,
- Sodium
- Calcium (total)
- Amylase
- Lipase



- Calcitonin
- Creatinine, including eGFR (per CKD-EPI)<sup>1</sup>

Haematology:

- Haemoglobin
- Haematocrit
- Erythrocytes
- Thrombocytes
- Leucocytes

Pregnancy test (females of child bearing potential):

- Serum beta-human chorionic gonadotropin (V1, V8, V10/V10A)
- Urine dip stick (V2)

**Calcitonin**

Blood samples for the measurement of calcitonin concentration will be drawn as per flow chart (see section [2](#)). In case any calcitonin value at any time of the trial is  $\geq 10$  ng/L, the algorithm in [appendix A](#) should be followed.

**Pregnancy testing**

Females of childbearing potential will have a serum pregnancy test performed. At the randomisation visit, a urine pregnancy test must be performed prior to randomisation.

In case a menstrual period is missed or if pregnancy is suspected at any time during the trial, a urine pregnancy test should be performed. The subject should be instructed not to dose trial product before pregnancy has been ruled out.

Pregnancy testing will not be required (unless required by local law) for women of non-childbearing potential, such as but not limited to women who have undergone a hysterectomy, bilateral oophorectomy, bilateral tubal ligation or are postmenopausal (e.g. women above the age of 50, who have been without menstrual period for at least 1 year), see section [8.2.6](#).

## **8.6 Other assessments**

### **8.6.1 Subject diary**

The subject must be provided with paper diaries at visits described in the flow chart. If a subject prematurely discontinues trial product, diaries, should be not be dispensed and completed by the subject after follow-up-premature discontinuation visit (P11A). Entries in the diaries are only to be made by the subject, unless otherwise specified.

The investigator should instruct the subject in recording the following data in the diary:

- Date, time and dose of first dose of trial product
- Date and last dose of trial product prior to each visit
- SMPG 7-point profile
- Hypoglycaemic episodes
- Concomitant medication
- AEs

The diaries should be handed out/collected as indicated in the flow chart. The subject should bring the diary for review at every clinic visit up until end of treatment visit (V10). The recordings must be reviewed as described in section [8.1.10](#) and transcribed to the eCRF.

If any hypoglycaemic events are reported at P11 or P11A, the information related to the hypoglycaemic event(s) should be documented in the subject's medical record and the entry in the medical record will be considered source data.

## **8.6.2 Electronic patient reported outcome questionnaires**

The following PRO questionnaire will be used in the trial:

SF-36v2™

DTSQ

CoEQ

The questionnaires should be completed by the subject as specified in the flow chart, see section [2](#), preferably after conclusion of all fasting related activities but before any other visit-related activities. It takes approximately 15 minutes to complete the questionnaires, see Section [13.3](#). Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. The assessments must be reviewed as described in Section [8.1.10](#).

### **8.6.2.1 SF-36v2**

The SF-36v2™ questionnaire will be used to assess subjects overall health related quality of life and can also be used to estimate quality adjusted life years (QALY) which is used in cost effectiveness calculations. This questionnaire contains 36 items and measures the individual overall health related quality of life on 8 domains; physical functioning, role functioning, body pain, general health, vitality, social functioning, role emotional and mental health.

### **8.6.2.2 DTSQs**

The DTSQs questionnaire will be used to assess subject's treatment satisfaction. This questionnaire consists of 8 items and measures the subject's diabetes treatment (including insulin, tablets and/or diet in terms of convenience, flexibility and general feelings regarding treatment).

### **8.6.2.3 Control of Eating Questionnaire (CoEQ)**

The CoEQ has its origin in the Food Craving Record. It comprises of 21-items designed to assess the intensity of food cravings, as well as subjective sensation of appetite and mood. For this trial a version with only 19 items will be included.

### **8.6.3 Training in the PDS290 pen-injector**

The subjects must be trained in how to handle the PDS290 pen-injector when handed out the first time. Training should be repeated during the trial at regular intervals at the discretion of the investigator in order to ensure correct use of the device. The training should be done in accordance with the directions for use.

### **8.6.4 Training in blood glucose meter use**

The subjects must be provided with a BG meter at visit 1 and instructed in how to use and handle the BG meter, in accordance with the flow chart (see section [2](#)). The subjects will be instructed in how to use the device and the instruction will be repeated at visit 2 and thereafter as necessary during the trial.

## **8.7 Subject compliance**

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

**Treatment compliance:** will be assessed by monitoring of drug accountability. Prior to visits where drug accountability is performed the subject will be asked to return all used, partly used and unused trial products. The investigator must assess the amount of trial products returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject.

## 9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the Trial Materials Manual (TMM).

The trial products will be dispensed to each subject as required according to treatment group. The IWRS will allocate trial product Dispensing Unit Number (DUN) to the subject at each dispensing or randomisation visit. The correct DUN must be dispensed to the subject.

If additional medication is needed, the IWRS must be contacted in order to have correct medication allocated.

Trial products must not be dispensed to any person not included in the trial.

Semaglutide must not be used, if it does not appear clear, colourless, or almost colourless.

### 9.1 Trial products

The following trial products will be provided by Novo Nordisk A/S, Denmark:

**Table 9–1 Trial products**

Trial product	Strength	Dosage form	Route of administration	Container/delivery device
Semaglutide 1.34 mg/mL	1.34 mg/mL	Solution for injection	Subcutaneous	1.5 mL PDS290 pre-filled pen-injector
Semaglutide placebo	N/A			
Canagliflozin 100 mg	100 mg	Tablet	Oral	Blister pack
Canagliflozin placebo	N/A			
Canagliflozin 300 mg	300 mg			
Canagliflozin placebo	N/A			

Background medication is defined as antidiabetic treatment with metformin. All randomised subjects must continue their antidiabetic pre-trial background medication throughout the entire duration of the trial, unless rescue criteria are met or a safety concern arises. As metformin is considered background medication (non-investigational medicinal product), it will not be provided by Novo Nordisk. However, metformin will be reimbursed if required by the country's Health Authority or IEC/IRB.

Semaglutide 1.34 mg/mL and semaglutide placebo are visually identical and will be packed blinded.

Canagliflozin 100/300 mg drug and corresponding placebo will be packed blinded. There are 2 different placebos: 1 for each of the respective doses of canagliflozin (100 mg and 300 mg).

## 9.2 Labelling

The trial products will be labelled in accordance with Annex 13<sup>44</sup>, local regulations and trial requirements. Each box will be labelled with a unique (DUN).

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to enrolment and randomisation.

The investigator must document that directions for use (DFU) is given to the subject orally and in writing at the first dispensing visit (randomisation visit, V2).

*For Argentina only: Glucose-lowering background medication and rescue medication, if applicable, will be reimbursed by Novo Nordisk Pharma Argentina S.A.*

## 9.3 Storage

**Table 9–2 Storage conditions**

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time <sup>a</sup>
Semaglutide 1.34 mg/mL	Store in refrigerator (2–8°C) Do not freeze Protect from light	Store below 30°C Do not freeze Protect from light	8 weeks
Semaglutide placebo			
Canagliflozin 100 mg	Do not store above 30°C Do not freeze Protect from light	N/A	N/A
Canagliflozin placebo			
Canagliflozin 300 mg			
Canagliflozin placebo			

<sup>a</sup> In-use time starts in the subjects home when the product is taken out of the refrigerator.

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the TMM.

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

#### **9.4 Drug accountability and destruction**

Drug accountability of all trial products received at site is the responsibility of the investigator.

Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at End of Treatment visit (please see flow chart, section [2](#)).

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

Non-allocated trial products including expired or damaged products must be accounted as unused at the latest at closure of the trial site.

Drug accountability should be performed at pen level for semaglutide/placebo, and at tablet level for Canagliflozin/placebo.

Destruction of trial products can be performed on an on-going basis and will be done according to local procedures after accountability is finalised and reconciled by the monitor. Destruction of products must be documented in the IWRS.

#### **9.5 Auxiliary supplies**

The following auxiliary supplies will be supplied by Novo Nordisk in accordance with the TMM:

- DFU for PDS290 pen-injector
- Needles for PDS290 pen-injector
- BG-meter and BG-meter related auxiliaries

Only needles provided by Novo Nordisk must be used for administration of trial product.

## 10 Interactive voice/web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Dispensing Verification (when barcode scanner is used)
- Treatment discontinuation
- Completion
- Code break
- Drug accountability
- Data change

IWRS user guides and worksheets will be provided to each trial site.

## 11 Randomisation procedure and breaking of blinded codes

This is a double-blind, two-arm parallel-group trial. A randomisation session will be performed for all eligible subjects by using IWRS.

At the randomisation visit (V2), eligible subjects will be randomised to one of the two parallel treatment groups in a 1:1 manner:

- semaglutide 1.0 mg once-weekly + canagliflozin placebo
- canagliflozin 300 mg once-daily + semaglutide placebo

The randomisation will be stratified according to the participation in the DXA scan sub-study (yes or no) in order to ensure balanced treatment allocation within the sub-study.

When a subject is randomised he/she must be assigned the lowest available randomisation number.

### 11.1 Breaking of blinded codes

The IWRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken. However, if the code is broken by Global Safety, the monitor will not be notified.

The code for a particular subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Whenever a code is broken the person breaking the code must print the Code Break Confirmation Notification generated by the IWRS, and sign and date the document. The reason for code break should be documented in the medical record.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IWRS is not accessible at the time of code break the IWRS helpdesk should be contacted. Contact details are listed in [attachment 1](#).

If the code has been broken by the investigator, the subject must discontinue treatment with trial product and a treatment discontinuation session must be completed in IWRS.



## 12 Adverse events, technical complaints and pregnancies

### 12.1 Definitions

#### 12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see Section [8.4.6](#)

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild** – no or transient symptoms, no interference with the subject's daily activities.
  - **Moderate** – marked symptoms, moderate interference with the subject's daily activities.
  - **Severe** – considerable interference with the subject's daily activities; unacceptable.
- **Causality**  
Relationship between an AE and the relevant trial products):
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.
  - **Unlikely** - The event is most likely related to aetiology other than the trial product.

- **Final outcome**

- **Recovered/resolved** - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
- **Recovering/resolving** - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae** - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
- **Fatal** - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as “recovered/resolved”, “recovering/resolving”, “recovered/resolved with sequelae” or “not recovered/not resolved”. An AE with fatal outcome must be reported as an SAE.
- **Unknown** - This term is only applicable if the subject is lost to follow-up.

### 12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death.
- A life-threatening<sup>a</sup> experience.
- In-patient hospitalisation<sup>b</sup> or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity<sup>c</sup>.
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening<sup>a</sup> or require hospitalisation<sup>b</sup> may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE<sup>d</sup>.

<sup>a</sup> The term “life threatening” in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

<sup>b</sup> The term “hospitalisation” is used when a subject:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social

purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

- <sup>c</sup> A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).
- <sup>d</sup> For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The following adverse events must always be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

- suspicion of transmission of infectious agents via the trial product
- risk of liver injury defined as ALT or AST >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

Additional assessments should be made for events meeting the criterion of Hy's law as stated above (see [appendix B](#)).

### **12.1.3 Non-serious adverse event**

A non-serious AE is any AE which does not fulfil the definition of an SAE.

### **12.1.4 Medication errors**

A medication error concerning trial products is defined as:

- Administration of wrong drug.  
Note: Use of wrong DUN is not considered a medication error.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product.
- Accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

Medication errors must be reported on an AE form and a specific event form, see Section [8.4.5.1](#).

### **12.1.5 Adverse events requiring additional data collection**

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial product.

In this trial the following AEs require the completion of specific event forms in the eCRF, see [Table 12-1](#)

**Table 12-1 Adverse events requiring completion of specific event forms and/or are subject to event adjudication**

Event	Specific event form	Event adjudication
Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)	Yes	Yes
Cerebrovascular event (stroke or transient ischaemic attack)	Yes	Yes
Heart failure	Yes	Yes (only if requiring hospitalisation)
Hypersensitivity reaction	Yes	No
Neoplasm (excluding thyroid neoplasm)	Yes	Yes (only if malignant)
Pancreatitis	Yes	Yes (only if acute pancreatitis)
Renal Event	Yes	No
Thyroid disease (including thyroid neoplasm)	Yes	Yes, (only if malignant thyroid neoplasm or C-cell hyperplasia)
Death	No	Yes
Hepatic event defined as: ALT or AST >5 x UNL and total bilirubin ≤ 2 x UNL ALT or AST >3 x UNL and total bilirubin >2 x UNL Hepatic event leading to trial product discontinuation	Yes	No
Diabetic retinopathy	Yes	No
Laboratory outlier	Yes	No

For details about specific event forms, see [appendix B](#)

### 12.1.6 Technical complaints

A technical complaint is any written, electronic, or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- All packaging material including labelling

- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle).

## 12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent (V1) until the end of the post-treatment follow-up period (P11). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and [Figure 12-1](#).

During each contact with the trial site staff, the subject must be asked about AEs and technical complaints, for example by asking: “Have you experienced any problems since the last contact?”

All AEs, observed by the investigator or subject, must be reported by the investigator and evaluated.

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a SIF must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one SIF can be used to describe all the SAEs.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest.

Some events will undergo event adjudication by the Event Adjudication Committee (EAC), please refer to Section [12.7.2](#). For AEs qualifying for event adjudication, the Adjudication Form will also have to be completed in the eCRF. The Adjudication Form is a checklist of clinical data to be provided from the site.

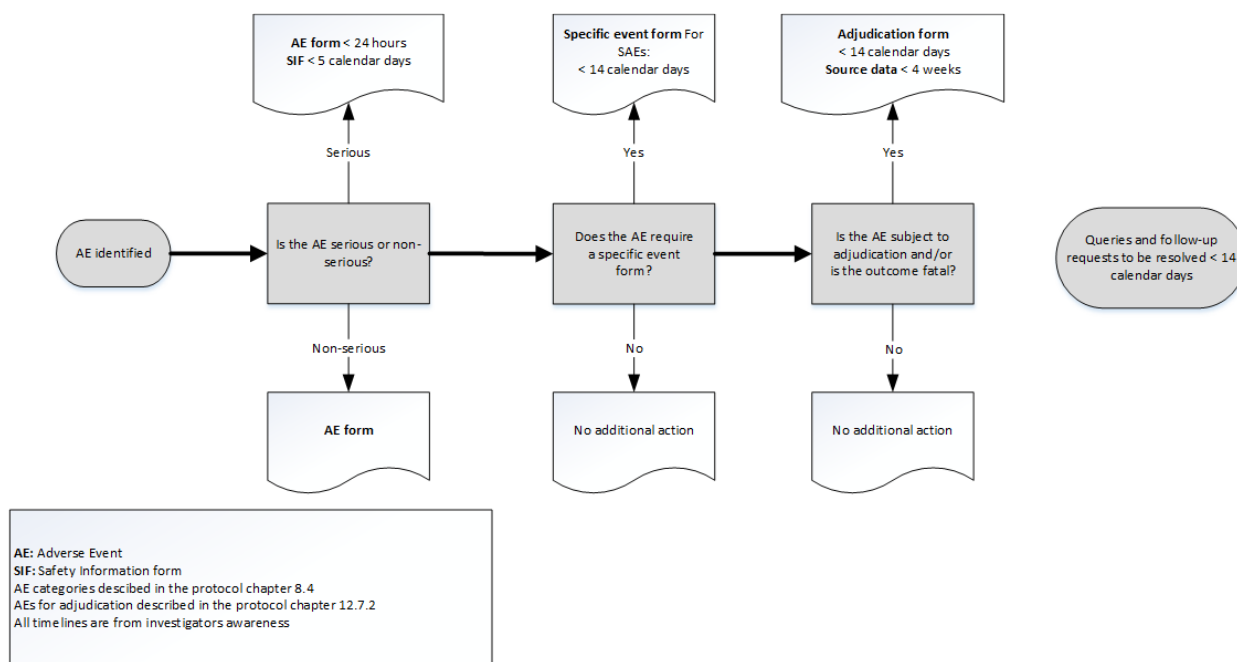
### Timelines for initial reporting of AEs:

The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the SIF **within 5 calendar** days of the investigator’s first knowledge of the SAE.
- **For SAEs requiring reporting on a specific event form:** In addition to the above the specific event form **within 14 calendar days** from the investigator’s first knowledge of the AE.
- **Events for adjudication:** The adjudication form should be completed within 14 calendar days of investigator’s first knowledge of the AE, see Section [12.7.2](#). The investigator should preferably provide the medical documentation within 4 weeks of event identification according to instructions in the event adjudication site manual.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.



**Figure 12–1 Reporting of AEs**

### **Novo Nordisk assessment of AE expectedness:**

Novo Nordisk assessment of AE expectedness is performed according to the following reference documents:

- Semaglutide: NN9535 IB<sup>25</sup> current version and any updates thereto
- Canagliflozin: Current version of the Invokana SmPC and any updates thereto<sup>32</sup>.

### **Reporting of trial product-related SUSARs by Novo Nordisk:**

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP<sup>2</sup>. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP<sup>2</sup>, unless locally this is an obligation of the investigator.

### **Novo Nordisk products used as concomitant medication**

If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

## **12.3 Follow-up of adverse events**

The investigator must record follow-up information by updating the forms in the eCRF.

Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the event is “recovered/resolved”, “recovered/resolved with sequelae” or “fatal”, and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering/resolving” or “not recovered/not resolved”. Cases can be closed with the outcome of “recovering/resolving” when the subject has completed the follow-up period and is expected by the investigator to recover.

The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator’s first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is “recovering/resolving”, “recovered/resolved” or “recovered/resolved with sequelae” or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering/resolving” or “not recovered/not resolved”. Cases can be closed with the outcome of “recovering/resolving” when the subject has completed the follow-up period and is expected by the investigator to recover.

The investigator must ensure that the recording of the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

**SAEs after end of trial:** If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a subject after the subject has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

## **12.4 Technical complaints and technical complaint samples**

### **12.4.1 Reporting of technical complaints**

All technical complaints on any of the following products:

- Semaglutide 1.34 mg/mL or placebo, 1.5 mL pen-injector
- Canagliflozin 100 mg or placebo tablets (blister pack)
- Canagliflozin 300 mg or placebo tablets (blister pack)
- Novo Nordisk needles for prefilled PDS290 pen-injector

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Centre, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in [attachment 1](#) to the protocol.

The investigator must assess whether the technical complaint is related to any AEs and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each code or lot number must be completed



The investigator must complete and forward the technical complaint form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints within **5 calendar days**

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

#### **12.4.2 Collection, storage and shipment of technical complaint samples**

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in [attachment 1](#)) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the code or lot number and, if available, the DUN. All parts of the DUN should be returned.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

### **12.5 Pregnancies**

#### **12.5.1 Pregnancies in female subjects**

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who have received trial product(s).

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age.

The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant.

The following must be collected and reported by the investigator to Novo Nordisk - electronically (e.g. in PDF format), or by fax or courier:

### 1. Reporting of pregnancy information

Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.

### 2. Reporting of AE information

The investigator has to report AEs in connection with the pregnancy as well as in the foetus and newborn infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous abortion), and congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE.

### Forms and timelines for reporting AEs:

Non-serious AEs:

- AE form<sup>a</sup> **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

- AE form<sup>a</sup> **within 24 hours** of the investigator's first knowledge of the SAE.
- SIF **within 5 calendar days** of the investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

<sup>a</sup> It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or newborn infant. If the AE occurred in the foetus or newborn infant, the AE can only be reported on paper AE and safety information form.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

## **12.6 Precautions and/or overdose**

Events of nausea, vomiting and headache have been reported in connection with accidental administration of semaglutide doses up to 4 mg. No symptoms of hypoglycaemia have been reported in connection with overdose of semaglutide. In the event of overdosage, appropriate supportive treatment should be initiated according to subject's clinical signs and symptoms.

## **12.7 Committees related to safety**

### **12.7.1 Novo Nordisk safety committee**

Novo Nordisk will constitute an internal semaglutide safety committee to perform ongoing safety surveillance. The semaglutide safety committee may recommend unblinding of any data for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

### **12.7.2 Event adjudication committee**

An independent external EAC is established to perform validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE. Pre-defined clinical data consist of copies of source documents collected and delivered by the investigational sites.

The EAC is composed of permanent members covering required medical specialities. EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk.

The events are reviewed by the EAC in a blinded manner. The EAC will have no authorisations to impact on trial conduct, trial protocol or amendments.

The EAC works in accordance with written guidelines included in the EAC Charter describing in details the composition, tasks, responsibilities and work processes of the committee.

The events outlined in Section [12.1.5](#) have been selected for adjudication in order to obtain an external independent validation of the diagnosis. In addition, cardiovascular events are being adjudicated according to Standardized Definitions<sup>45</sup>.

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (e.g. x-ray, ECGs, ultrasound images, discharge summaries, pathology reports and death certificates). The investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk or the event adjudication vendor.

The AEs for adjudication are listed in [Table 12–2](#)

**Table 12–2 Adverse events for adjudication**

Events	Description	Adjudication outcome
Death*	<ul style="list-style-type: none"> <li>All-cause death</li> </ul>	<ul style="list-style-type: none"> <li>Cardiovascular death (including undetermined cause of death)</li> <li>Non-Cardiovascular death</li> </ul>
Acute Coronary Syndrome	Acute Coronary Syndrome conditions include: <ul style="list-style-type: none"> <li>ST-elevation acute myocardial infarction (STEMI)</li> <li>Non-ST elevation acute myocardial infarction (NSTEMI)</li> <li>Silent MI</li> <li>Unstable angina pectoris (UAP) requiring hospitalisation</li> </ul>	<ul style="list-style-type: none"> <li>Acute myocardial infarction (STEMI or NSTEMI), silent MI</li> <li>Unstable angina pectoris requiring hospitalisation</li> </ul>
Cerebrovascular events	<ul style="list-style-type: none"> <li>Episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction</li> <li>Transient Ischaemic Attack (TIA) is defined as a transient episode (&lt;24 hours) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction</li> </ul>	<ul style="list-style-type: none"> <li>Ischaemic stroke</li> <li>Haemorrhagic stroke</li> <li>Undetermined stroke</li> <li>TIA</li> </ul>
Heart failure requiring hospitalisation	<ul style="list-style-type: none"> <li>Hospitalisation with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)</li> </ul>	<ul style="list-style-type: none"> <li>Heart failure requiring hospitalisation</li> </ul>
Acute pancreatitis	The diagnosis of acute pancreatitis requires two of the following three features: <ul style="list-style-type: none"> <li>Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)</li> <li>Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal</li> <li>Characteristic findings of acute pancreatitis on imaging</li> </ul>	<ul style="list-style-type: none"> <li>Acute pancreatitis               <ul style="list-style-type: none"> <li>Mild</li> <li>Moderate severe</li> <li>Severe</li> </ul> </li> </ul>
Malignant neoplasm	Malignant neoplasms are defined as: <ul style="list-style-type: none"> <li>Neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems</li> <li>Thyroid neoplasms are excluded in this event category</li> </ul>	<ul style="list-style-type: none"> <li>Malignant neoplasm</li> </ul>
Thyroid disease, if malignant thyroid neoplasm or C-cell hyperplasia	<ul style="list-style-type: none"> <li>Malignant thyroid neoplasms are defined as thyroid neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems</li> <li>C-cell hyperplasia, defined as hyperplasia of the parafollicular C-cells of the thyroid gland</li> </ul>	<ul style="list-style-type: none"> <li>Malignant thyroid neoplasm</li> <li>C-cell hyperplasia</li> </ul>

\*Death is not a separate event, but an outcome

There are different processes for capturing events for adjudication:

- Direct reporting by investigator:
  - All AEs need to be assessed by the investigator if any AE category is applicable. If the AE category selected is in scope for adjudication, the event specific adjudication form will be populated for sites to complete
  - AEs with fatal outcome
- Screening:
  - All AEs will be screened by NN for potential missed events for adjudication and if needed, the investigator will be asked to provide additional information such as an alternative aetiology, underlying cause(s) and/or clinical details.
- EAC identified events:
  - The EAC can decide to have an AE adjudicated even if not initially reported as an event for adjudication by the investigator.

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures.

The assessment made by the EAC will be included in the clinical trial report as well as the assessments made by the investigator. However, the adjudication made by the (EAC), given its independent analysis of each event, will be attributed with greater importance of the two. The outcome of adjudication will be kept in the clinical trial database.

## 13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms

The following will be provided as paper CRFs to be used when access to the eCRF is revoked or if the eCRF is unavailable:

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints that are not subject related (e.g. discovered at trial site before allocation))

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the paper CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing “NA” (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the paper CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

### 13.1 Corrections to case report forms

Corrections to the eCRF data may be made by the investigator or the investigator’s delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the investigator’s delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

### **13.2 Case report form flow**

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

The pregnancy forms are paper based CRFs. Also, the AE forms, technical complaint forms, and safety information forms will be provided in paper but are only to be used if for any reason the eCRF is unavailable.

The investigator must ensure that data is recorded in these forms as soon as possible after the visit.

At the end of the trial the investigator must ensure that all remaining data have been entered into the eCRF no later than 3 days after Last Patient Last Visit (LPLV) at the site in order to ensure the planned lock of the database.

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

### **13.3 Electronic collection of questionnaires**

Novo Nordisk will use a tablet computer at sites for electronic recording of PRO questionnaires (see Section [8.6.2](#)). The tablet computer and related support services will be supplied by an external vendor.

Subjects will be instructed in the use of the tablet computer before entering any data. The tablet computer will contain built-in edit checks, to ensure that all relevant questions are answered. The tablet computer is not intended to support the subsequent review and modification of completed entries. In case of need for corrections to the transferred data, a query flow must be initiated by the investigator or delegate. An audit trail will be maintained.

All data entered will be transferred automatically from the tablet computer to a database hosted by the supplier which is considered source data. Data entered on the devices will upon confirmation of successful backup be deleted from the devices.

Data in this database will be viewable to relevant site and Novo Nordisk personnel through a secure and password-protected web portal. Data will be transferred to the Novo Nordisk clinical database at defined intervals.

Site-specific electronic questionnaire data (in an electronic readable format) will be provided to the trial site before access to the supplier database is revoked. This data must be retained at the trial site.

## 14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than 4 weeks after, this will include a visit at the DXA radiology unit as well. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LPLV at the trial site. The on-site monitoring visit interval to the DXA radiology unit must not exceed 6 months at sites with active subjects.

The monitor must be given direct access to all source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

All data must be verifiable in source documentation other than the eCRF.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The original of the completed diaries and ePROs (tablets) must not be removed from the trial site, unless they form part of the CRF/eCRF and a copy is kept at the site.

All data entered will be automatically transferred from the device to the ePRO database, hosted by the supplier. This database is considered as the source. The monitor will ensure that the eCRFs are completed and that paper CRFs are collected.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent.
- Reason for screening failure

Monitors will review the subject's medical records and other source data (e.g. the diaries and ensure ePROs are completed) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.



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A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

## 15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a CRO.

In cases where data management activities are delegated to external vendors, there will be regular transfer of data during the trial.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

## 16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

## 17 Statistical considerations

### 17.1 General considerations

No interim analyses or other analyses of un-blinded or between group data will be performed before the database is locked.

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

Laboratory values below the lower limit of quantification (LLOQ) will be set to  $\frac{1}{2}$ LLOQ.

Results from a statistical analysis will be presented by the estimated treatment contrasts at week 52 with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference if not otherwise specified.

The comparison presented from a statistical analysis will be semaglutide 1.0 mg versus canagliflozin 300 mg

If no statistical analysis is specified, data will be presented using relevant summary statistics.

Data from all trial sites will be analysed and reported together.

The regions used in the statistical analyses are defined as:

- North America (USA and Canada)
- Region Europe (UK, Ireland, Italy and Sweden)
- International Operations (Lebanon, Malaysia, Argentina, Mexico, Brazil, India)

#### 17.1.1 Data transformations

A number of the continuous parameters will be log-transformed prior to statistical analysis. The output tables and figures will show the results of the analysis back-transformed to the original scale, implying that log-treatment-differences are reported as treatment ratios. Confidence intervals for the treatment ratios will be calculated as exponentiated upper and lower limits for log-treatment difference confidence intervals. The standard errors (SE) of the back-transformed mean and ratio to baseline estimates are also provided; these SEs are calculated using the delta-method (first order Taylor approximation), whereby the SE on the original scale is calculated as the product of the SE on log-scale and the exponentiated estimate of the mean (geometric mean).

### **17.1.2 Definition of baseline**

For each assessment, the baseline assessment is defined as the latest available measurement at or prior to the randomisation visit. This specifically implies that if a visit 2 assessment is missing (whether it was planned or not planned) then the screening assessment (from visit 1), if available, will be used as the baseline assessment.

### **17.1.3 Primary estimand**

To further detail the trial objective an estimand is defined which is a *de-jure* (efficacy) estimand:

#### **1. Primary estimand**

- The treatment difference between semaglutide and canagliflozin at week 52 for all randomised subjects if all subjects completed treatment and did not initiate rescue medication

This primary *de-jure* estimand is considered clinically relevant as it assesses the glycaemic benefit a person with T2D is expected to achieve if initiating and continuing treatment with semaglutide compared to canagliflozin. Accordingly, only data collected prior to discontinuation of trial product or initiation of rescue medication will be used to draw inference. This will avoid confounding from rescue medication.

### **17.1.4 Trial completion**

Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial. The full duration of the trial is defined as up to and including the follow-up visit (P11). Subjects completing the follow-up visit (P11) will be considered trial completers.

### **17.1.5 Missing data considerations at week 52**

The actual rate of missing data at week 52 is expected to be maximum 10% based on the rate of trial completers from the subcutaneous semaglutide phase 3a clinical development program. The frequency of missing data is expected to be similar in the semaglutide and the canagliflozin groups.

When estimating the primary estimand, the combined rate of missing data, subjects discontinuing treatment prematurely or initiating rescue medication on top of trial product, is expected to be maximum 30%. This is based on the results from the subcutaneous semaglutide phase 3a clinical development program. Based on these data, premature treatment discontinuation due to gastrointestinal adverse events is expected to be low but more frequent in semaglutide compared to canagliflozin. Other reasons for discontinuing treatment are assumed to be unrelated to treatment and therefore occur with similar rates, so overall the frequency of missing data or data not used at week 52 in the primary analysis is expected to be slightly larger in semaglutide as compared to canagliflozin.

To document the extent and reason(s) for missing data, descriptive summaries and graphical representation of extent, reason(s) for and pattern of missing data will be presented by treatment group.

## 17.2 Sample size calculation

The primary endpoint, change from baseline to week 52 in HbA<sub>1c</sub> (%) will be tested for non-inferiority and superiority of semaglutide vs. canagliflozin. The confirmatory secondary endpoints, change from baseline to week 52 in body weight (kg) and change from baseline to week 52 in total fat mass (kg) are planned to be tested for superiority of semaglutide vs. canagliflozin.

The sample size calculation is made to ensure a power of at least 90% for meeting HbA<sub>1c</sub> superiority of semaglutide vs. canagliflozin out of the four pre-specified confirmatory hypotheses shown in [Table 17-1](#). The closed testing procedure described in Bretz et.al. 2011<sup>46</sup> combined with a hierarchical approach is used to control the overall type-1 error at a nominal two-sided 5% level. The statistical testing strategy is built on the following principle:

- Glycaemic efficacy must be established by HbA<sub>1c</sub> non-inferiority before testing for added benefits in terms of superiority in terms of HbA<sub>1c</sub> or body weight.
- HbA<sub>1c</sub> and body weight superiority must be established before testing for added benefits in terms of superiority in terms of total fat mass.

The sample size is calculated using the calcPower function in the R package, gMCP<sup>47</sup> using 10,000 simulations. All of the four pre-specified confirmatory tests are assumed to be independent. Since some of these tests are positively correlated, the assumption of independence is viewed as conservative. The four hypotheses are:

- HbA<sub>1c</sub> non-inferiority of semaglutide 1.0 mg vs. canagliflozin 300 mg with a non-inferiority margin of 0.3
- HbA<sub>1c</sub> superiority of semaglutide 1.0 mg vs. canagliflozin 300 mg
- Body weight superiority of semaglutide 1.0 mg vs. canagliflozin 300 mg
- Total fat mass superiority of semaglutide 1.0 mg vs. canagliflozin 300 mg

The sample size assumptions for efficacy based on on-treatment data without rescue medication, a treatment effect based on in-trial data (see Section [17.3.1](#)) and the standard deviations (SD) are given in [Table 17-1](#). The HbA<sub>1c</sub> and body weight assumptions are based on the efficacy results and an observed reduction of approximately 20% and 15% respectively in in-trial treatment effect compare to efficacy in the subcutaneous semaglutide phase 3a clinical development programme<sup>28, 48-52</sup>.

A similar reduction in the in-trial treatment effect compared to efficacy is assumed with canagliflozin as comparator. The total fat mass assumption is based on the relevant literature

focusing on fat mass<sup>53-55</sup>, which indicates a smaller SD for total fat mass as compared to body weight.

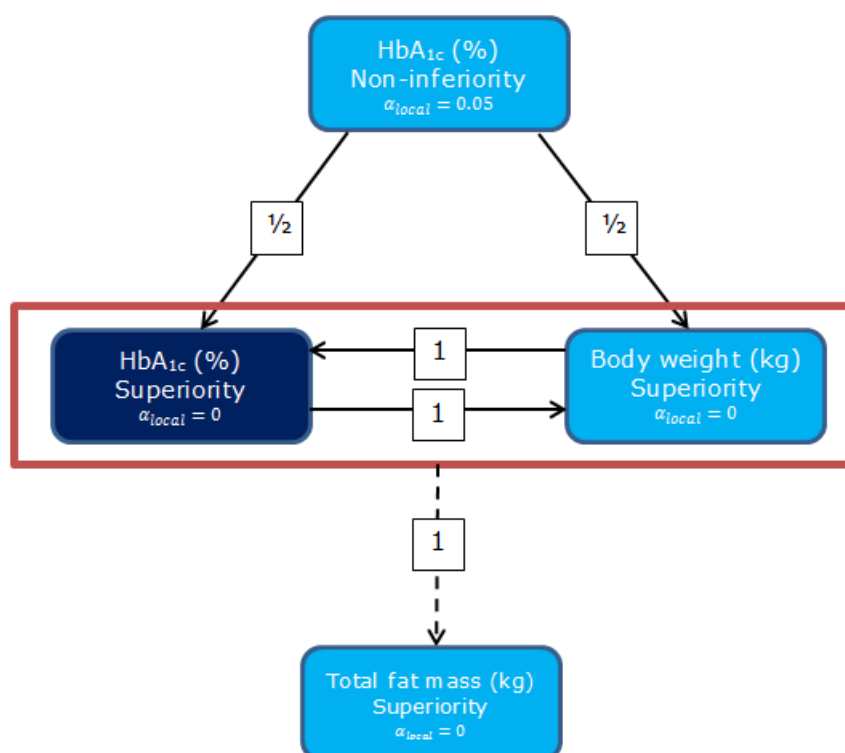
**Table 17–1 Assumptions used in the sample size calculation**

Semaglutide vs. canagliflozin	HbA <sub>1c</sub>	Body weight	Total fat mass
Efficacy	-0.32%	-2.4 kg	-1.8 kg
In-trial treatment effect	-0.256%	-2.04 kg	-1.53 kg
Standard deviation	1.1%	4.0 kg	3.5 kg

With the above assumptions, allocating 392 subjects to the semaglutide arm and the canagliflozin arm provides 90% power to confirm HbA<sub>1c</sub> superiority of semaglutide vs. canagliflozin across plausible assumptions.

**Table 17–2 Calculated powers for meeting individual hypotheses**

Statistical test	HbA <sub>1c</sub> non- inferiority	HbA <sub>1c</sub> superiority	Body weight superiority	Total fat mass superiority
Efficacy Power (%)	>99%	90%	>99%	91%
In-trial effect power (%)	>99%	90%	>99%	74%



**Figure 17–1 Graphical illustration of the closed testing procedure.**

The overall significance level of  $\alpha = 0.05$  (two-sided) is initially allocated to the HbA<sub>1c</sub> non-inferiority test. The local significance level ( $\alpha$ -local) will be reallocated if a hypothesis is confirmed according to the weight given by the directed edges between nodes (hypotheses). The total fat mass superiority test will receive the overall significance of  $\alpha = 0.05$  (two-sided) if and only if both HbA<sub>1c</sub> and body weight superiority are confirmed at their respective local significance levels.

The overall significance level of  $\alpha = 0.05$  (two-sided) is initially allocated to the HbA<sub>1c</sub> non-inferiority test. The local significance level ( $\alpha$ -local) will be reallocated if a hypothesis is confirmed according to the weight given by the directed edges between nodes (hypotheses). The total fat mass superiority test will receive the overall significance of  $\alpha = 0.05$  (two-sided) if and only if both HbA<sub>1c</sub> and body weight superiority are confirmed at their respective local significance levels.

### 17.2.1 Sample size for the sub-study (DXA scan)

For the sub-study on body composition assuming an efficacy treatment difference of 1.8 kg and a SD of 3.5 kg, 174 subjects (87 subjects in each arm) will provide 92% power to establish a statistical significant difference resulting in 91% power for confirming superiority in the testing strategy in terms of fat mass loss (kg) at week 52 using a two-sided significance level of 5%.

### 17.3 Definition of analysis sets

The following analysis sets will be defined:

**Full analysis set (FAS):** includes all randomised subjects. Subjects in the FAS will contribute to evaluation “as randomised”.

**Safety analysis set (SAS):** includes all subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation based on the trial product received for the majority of the period they were on treatment. This will be referred to as contributing to the evaluation “as treated”.

**Per protocol (PP) analysis set:** includes all subjects in the FAS who fulfil the following criteria:

- Have not violated any inclusion criteria
- Have not fulfilled any exclusion criteria
- Have a non-missing HbA<sub>1c</sub> measurement at screening and/or randomisation
- Is on trial product at week 28 and have at least one non-missing HbA<sub>1c</sub> measurement at or after week 28

Subjects in the PP analysis set will contribute to the analysis “as treated” as defined for the SAS.

#### 17.3.1 Data selections and observation periods

Subjects and data to be used in an analysis will be selected in a two-step manner.

- Firstly, subjects will be selected based on the specified analysis set
- Secondly, data points on the selected subjects from first step will be selected based on the specified observation period

Definition of the observation periods:

**In-trial:** This observation period represents the time period where subjects are considered to be in the trial after randomisation, regardless of discontinuation of trial product or initiation of rescue medication. The in-trial observation period starts at randomisation (as registered in IWRS) and ends at the date of:

- The last direct subject-site contact, which is scheduled to take place 5 weeks after planned last dose of trial product at a follow-up visit
- Withdrawal for subjects who withdraw their informed consent
- The last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up
- Death for subjects who dies before any of the above

For subjects not randomised but exposed to trial product the in-trial period starts at the date of first dose of trial product



**On-treatment:** This observation period represents the time period where subjects are considered treated with trial product. The observation period is a sub-set of the in-trial observation period. It starts at the date of first dose of trial product. Two slightly different end dates will be needed to cover all assessments appropriately according to the flow chart. For adjudicated events, ECG's and AEs including hypoglycaemic episodes, the observation period ends at the first date of any of the following:

- the follow-up visit (P11)
- the follow-up prematurely discontinuation visit (P11A)
- the last date on trial product + 42 days
- the end-date for the in-trial observation period

The follow-up visit is scheduled to take place 5 weeks after the last date on trial product corresponding to approximately five half-lives of subcutaneous semaglutide. The visit window for the follow-up visit is + 7 days, which is the reason for the 42 days specified in the bullet above. Hence, for those assessments this period reflects the period in which subjects are exposed.

For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product + 7 days. This ascertainment window corresponds to the dosing interval and will be used to avoid attenuation of a potential treatment effect on endpoints for which the effect is reversible shortly after treatment discontinuation. Hence, for those assessments this period reflects the period in which subjects are treated.

**On-treatment without rescue medication:** This observation period is a sub-set of the on-treatment observation period, where subjects are considered treated with trial product, but have not initiated any rescue medications. Specifically it starts at date of first dose of trial product and the observation period ends at the first date of any of the following:

- the last dose of trial product +7 days
- initiation of rescue medication

The 'on-treatment without rescue medication' observation period will be the primary observation period for efficacy evaluations. The in-trial observation period will be considered supportive for efficacy evaluation. Safety will be evaluated based on the in-trial and the on-treatment observation periods unless otherwise specified.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period. For adjudicated events, the onset date will be the EAC adjudicated onset date.

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility

of the members of the Novo Nordisk study group.

Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion will be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

## **17.4 Primary endpoint**

The primary endpoint is change from baseline to week 52 in HbA<sub>1c</sub>.

### **17.4.1 Primary analysis for the primary estimand**

The primary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 52 from the 'on-treatment without rescue medication' observation period. Imputation of missing data will be handled using multiple imputation assuming that missing data is missing at random (MAR). Missing data will be imputed using observed data within the same group defined by the randomised treatment (semaglutide/canagliflozin). It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who receive the same treatment.

Technically missing values will be imputed as follows:

- Intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each of the treatment groups separately and 200 copies of the dataset will be generated
- A sequential regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and sequentially continuing to the last planned visit at week 52. A model used to impute missing values at each planned visit will be fitted for each of the treatment groups using observed data. The model will include stratification factor (sub-study, non-sub-study) and region as categorical effects and baseline and post-baseline HbA<sub>1c</sub> values observed prior to the visit in question as covariates.
- An ANCOVA with treatment, stratification factor (sub-study, non-sub-study) and region as categorical effects and baseline HbA<sub>1c</sub> as a covariate will be used to analyse HbA<sub>1c</sub> values at week 52 for each of the 200 complete data sets generated as part of the imputation of missing values. Rubin's rule will be used to combine the analysis results in order to draw inference.

From this analysis, the estimated treatment difference between semaglutide and canagliflozin at week 52 will be presented together with the associated two-sided 95% confidence interval and unadjusted two sided p-values for testing non-inferiority and superiority.

### 17.4.2 Primary hypotheses

For the primary HbA<sub>1c</sub> endpoint the following confirmatory one-sided hypotheses are planned to be tested for semaglutide versus canagliflozin. Let the mean treatment difference be defined as  $\mu =$  (semaglutide minus canagliflozin):

- Non-inferiority, using a non-inferiority margin of 0.3%
  - H0:  $\mu \geq 0.3\%$  against Ha:  $\mu < 0.3\%$
- Superiority
  - H0:  $\mu \geq 0.0\%$  against Ha:  $\mu < 0.0\%$

Operationally the hypotheses will be evaluated by two-sided tests.

The non-inferiority margin of 0.3 is chosen based on the diabetes guideline<sup>56, 57</sup> and the effect of canagliflozin on glycaemic effect seen in a similar trial (DIA3006) where canagliflozin was used as add on to metformin. In this trial canagliflozin showed an HbA<sub>1c</sub> treatment difference to placebo of -0.77%. Hence, based on this trial, the chosen margin of 0.3 provides assurance that semaglutide has an effect compared to placebo greater than 0 with a clinically relevant size. With regards to the constancy assumption, controlled clinical trials have consistently established that canagliflozin is an effective anti-diabetic drug. Therefore, lack of trial sensitivity with canagliflozin as comparator is not anticipated to be an issue in this trial.

### 17.4.3 Multiplicity and criteria for confirming hypotheses

The Type-I error for testing the four confirmatory hypotheses related to the HbA<sub>1c</sub>, body weight, and fat mass endpoints will be preserved in the strong sense at 5% (two-sided) using the weighted Bonferroni-based closed testing procedure described in Bretz et. al.<sup>46</sup> and outlined in [Figure 17-1](#). The first hypothesis to be tested is non-inferiority of HbA<sub>1c</sub>. It will be tested at the overall significance level (5%) while allocating 0% local significance level to the remaining three hypotheses. For this hypothesis, and in general, if a hypothesis is confirmed the significance level will be reallocated according to the weight and the direction of the edges going from the confirmed hypothesis to the next hypotheses as specified in [Figure 17-1](#). Total fat mass will be tested at the overall significance level if each of the other 3 hypotheses is confirmed, otherwise its local significance level will remain 0%. Each of the following hypotheses will be tested at their local significance level ( $\alpha$ -local). This process will be repeated until no further hypotheses can be confirmed.

Non-inferiority and subsequent superiority will be considered confirmed if the mean treatment difference is supporting the corresponding alternative hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below its local two-sided significance level as defined by the closed testing procedure in [Figure 17-1](#). This is equivalent to using a one-sided p-

value (nominal  $\alpha = 0.025$ ) and a one-sided 2.5% overall significance level in the closed testing procedure.

#### **17.4.4 Statistical subgroup analyses of HbA<sub>1c</sub>**

Five subgroups based on baseline HbA<sub>1c</sub> values are defined as follows:

1.  $\leq 7.5\%$
2.  $> 7.5\%$  to  $8.0\%$  (inclusive)
3.  $> 8.0\%$  to  $8.5\%$  (inclusive)
4.  $> 8.5\%$  to  $9.0\%$  (inclusive)
5.  $> 9.0\%$

Change from baseline in HbA<sub>1c</sub> at week 52 for subgroups based on baseline HbA<sub>1c</sub> values will be analysed for the primary estimand using a similar multiple imputation approach as described in section [17.4.1](#). The complete data sets from the primary analysis will be reused. However the ANCOVA model used to analyse the 200 complete data sets will additionally include the interaction effect of subgroup and treatment as a categorical effect. Rubin's rule will then be used to combine the results and the p-value for the interaction effect and estimated treatment differences at 52 weeks with corresponding two-sided 95% confidence intervals for each subgroup will be presented.

#### **17.4.5 Sensitivity analyses**

In order to investigate the robustness of the conclusions from the primary analysis and to stress test the MAR assumption for missing data tipping point sensitivity analyses will be performed for the primary estimand both for the sensitivity of the non-inferiority and the superiority HbA<sub>1c</sub> hypotheses.

##### **17.4.5.1 Sensitivity analyses for the primary estimand**

The estimation of the primary estimand will be repeated using the following sensitivity analysis:

- Tipping-point analysis (pattern mixture model based) based on the FAS using the 'on-treatment without rescue medication' observation period. In this analysis, subjects from the semaglutide group with missing observations will be given a penalty, i.e., it is assumed that subjects with missing observations who are randomised to semaglutide will receive a treatment that is worse than subjects with observed values who are randomised to semaglutide. The idea is to gradually increase the penalty to evaluate at which level the superiority conclusion of the analyses in terms of statistical significance is changed. The tipping point is the penalty level, at which the magnitude of efficacy reduction in subjects with missing data creates a shift in the treatment effect of semaglutide from being statistically significantly better than canagliflozin to being non-statistically significantly better for the superiority test and similarly for the non-inferiority test. Technically, this analysis will be implemented by replicating the primary analysis including

the assumption of MAR but subsequently adding increasing penalty values at week 52 to imputed observations in the semaglutide group before applying ANCOVA on the 200 complete data sets.

#### **17.4.5.2 Other sensitivity analyses**

The following additional sensitivity analyses are specified:

- In-trial treatment policy analysis based on the FAS using post-baseline measurements up to and including week 52 from the in-trial observation period. Missing data will be imputed using the same approach as described for the primary analysis of the primary estimand. However the imputation will be done within the same group defined not only by the randomised treatment (semaglutide/canagliflozin) but also by the status of treatment completion (still on randomised treatment at week 52 yes/no) (4 groups in total). It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who at week 52 are similar in terms of randomised treatment and treatment completion status. In addition in the imputation step stratification factor and region is not included in the model in order to avoid potential issues with sparse data. This analysis could be considered addressing an effectiveness estimand.
- PP analysis based on the PP data set using the ‘on-treatment without rescue’ observation period. This analysis will be carried out for non-inferiority testing only. The statistical analysis will be the same as the primary analysis for the primary estimand.

### **17.5 Secondary endpoints**

#### **17.5.1 Confirmatory secondary endpoints**

Change from baseline to week 52 in body weight (kg) and change from baseline to week 52 in total fat mass (kg) will be confirmatory secondary endpoints.

The primary estimand will be estimated using the same approach as described for the primary HbA<sub>1c</sub> endpoint. Body weight and total fat mass will be tested for superiority. Baseline and post-baseline body weight or total fat mass will be used as covariates instead of HbA<sub>1c</sub> for their respective analyses.

Superiority will be considered confirmed if the mean treatment difference is supporting the corresponding hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below its local two-sided significance level resulting from the closed testing procedure in [Figure 17-1](#).

The tipping point sensitivity analysis pre-specified to evaluate the robustness of the conclusions from the primary analysis of HbA<sub>1c</sub> will also be performed to evaluate the robustness of the

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conclusions from the body weight and total fat mass superiority tests. In addition, the in-trial sensitivity analysis will also be performed for both body weight and total fat mass.

## **17.5.2 Supportive secondary endpoints**

No sensitivity analyses are planned for the supportive secondary endpoints.

### **17.5.2.1 Efficacy endpoints**

#### **Continuous endpoints**

The continuous endpoints are change from baseline to week 52 in:

- Fasting Plasma Glucose (FPG)
- Self-Measured Plasma Glucose (SMPG), 7-point profile:
  - Mean 7-point profile
  - Mean post prandial increment (over all meals)
- Fasting blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)
- Body Mass Index (BMI) and waist circumference
- Systolic and diastolic blood pressure
- Body weight (%)
- Total fat mass (%)
- Total lean mass (kg)
- Total lean mass (%)
- Visceral fat mass (kg)
- Visceral fat mass (%)
- Ratio between total fat mass and total lean mass

The above continuous endpoints will be analysed for the primary estimand separately using a similar model approach as for the primary endpoint with the associated baseline and post-baseline responses as covariates instead of HbA1c for their respective analyses.

Fasting lipid profile endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

#### **Mean 7-point profile (SMPG) definition**

Subjects will be asked to perform SMPG measurements before and 90 minutes after breakfast, lunch, dinner, and at bedtime.

Mean of the 7-point profile is defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time.

## Binary endpoints

The binary endpoints are subjects who after 52 weeks treatment achieve (yes/no):

- HbA<sub>1c</sub> <7.0% (53 mmol/mol), American Diabetes Association (ADA) target
- HbA<sub>1c</sub> ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists (AACE) target
- Weight loss ≥3%
- Weight loss ≥5%
- Weight loss ≥10%
- HbA<sub>1c</sub> <7.0% (53 mmol/mol) without severe or blood glucose confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA<sub>1c</sub> reduction ≥1%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥3%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥5%
- HbA<sub>1c</sub> reduction ≥1% and weight loss ≥10%

The above 10 endpoints will be analysed for the primary estimand. The analyses for the primary estimand for all 10 endpoints will be based on the 'on-treatment without rescue medication' observation period. They will be analysed separately using the same type of logistic regression model with treatment, stratification factor (sub-study, non- sub-study), region and associated baseline and post-baseline response(s) (i.e. HbA<sub>1c</sub> responses for HbA<sub>1c</sub> endpoints, body weight responses for weight endpoints and both HbA<sub>1c</sub> and body weight responses for the binary endpoints that combine both parameters) as covariates. To account for missing data, the analysis will be made using a sequential multiple imputation approach as described below:

- Multiple imputed data sets (200) will be created in which missing values for the underlying continuous assessments are imputed by treatment group assuming MAR similar to the approach described for the primary analysis in section [17.4.1](#).
- The binary endpoint will be created for each of the 200 complete data sets
- Each of the created complete data sets will be analysed with the logistic regression model.

Estimated odds ratios will be log transformed and inference will be drawn using Rubin's rule<sup>58</sup>.

The results after applying Rubin's rule will be back-transformed and described by the odds ratio between treatments and the associated 95% confidence interval and p-value for no treatment difference.

### 17.5.2.2 Safety endpoints

The safety endpoints will be evaluated based on SAS using the on-treatment observation period and the in-trial observation period unless otherwise stated.



## Adverse Events

The following endpoint related to adverse events is used to support the safety objective;

- Number of treatment emergent adverse events (TEAEs)

A treatment-emergent AE is an event that has onset date (or increase in severity) during the on-treatment observation period. These will therefore be referred to as ‘on-treatment AEs’ hereafter. On-treatment adverse events are summarised descriptively in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). These summaries are replicated by outputs including all ‘in-trial’ adverse events (i.e., adverse events with onset date [or increase in severity] during the ‘in-trial’ observation period). Adverse events with onset after the end of the ‘in-trial’ observation period will be reported in a listing. The development over time in gastrointestinal AEs will be presented graphically.

The most frequent adverse events will be defined as preferred terms (PTs) that are experienced by at least 5% of the subjects in any of the treatment arms.

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

## Hypoglycaemic episodes

The following two endpoints related to hypoglycaemic episodes are used to support the safety objective:

- Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes
- Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes (yes/no)

Data on treatment-emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one episode, the percentage of subjects with at least one episode (%), the total number of episodes and the episode rate per 100 years of exposure. Summaries of treatment-emergent hypoglycaemic episodes will be presented as an overview including all episodes and episodes by severity.

### Classification of Hypoglycaemia:

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset is in the on-treatment period (see definition of observation period in section [17.3.1](#))

Nocturnal hypoglycaemic episodes: are episodes occurring between 00:01 and 05.59 both inclusive.

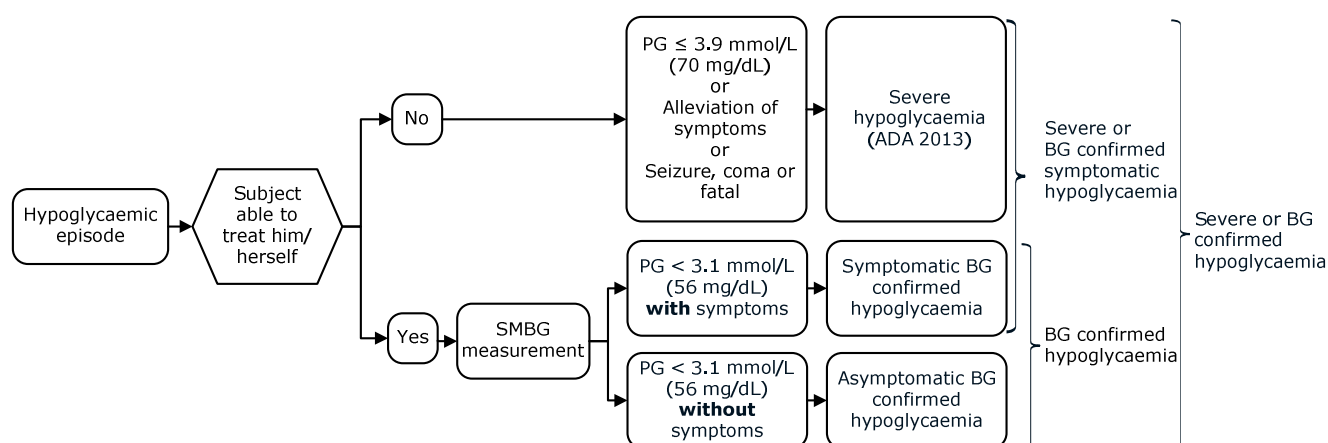
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see [Figure 17-2](#)) and the ADA classification of hypoglycaemia (see [Figure 17-3](#)).

### Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)<sup>59</sup>. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see [Figure 17-2](#)) in addition to the ADA classification:

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification<sup>60</sup> or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

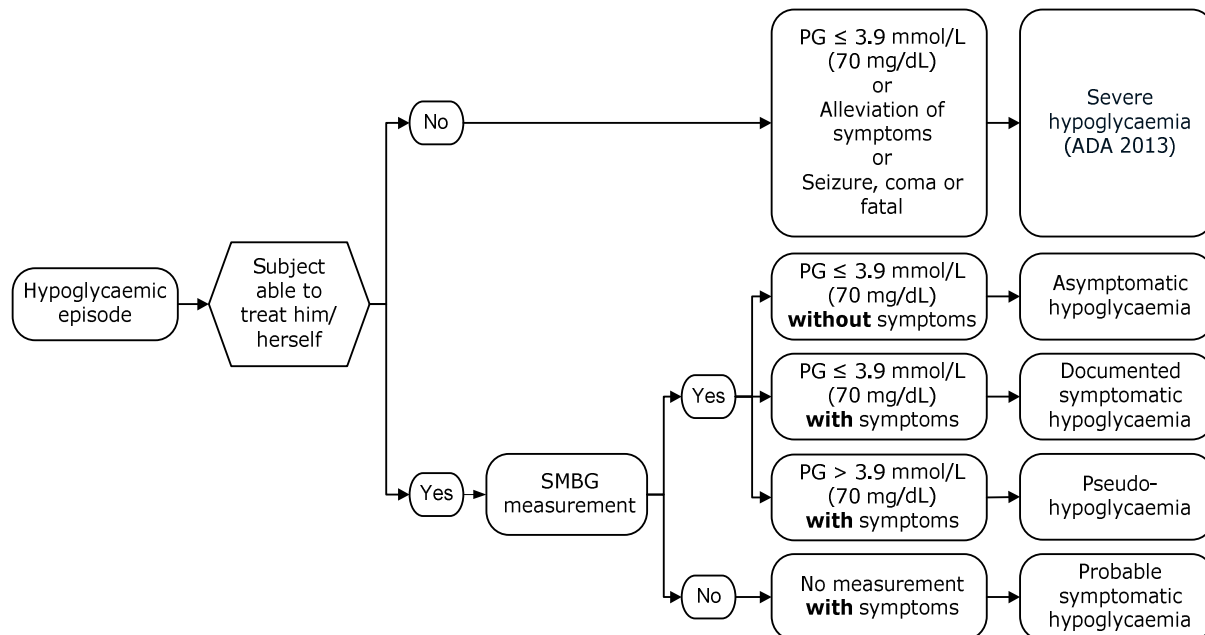


Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

**Figure 17-2 Novo Nordisk classification of hypoglycaemia**

### ADA classification<sup>60</sup> of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration  $> 3.9$  mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL).



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

**Figure 17–3 ADA classification of hypoglycaemia**

### **Number of treatment emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes**

Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 56 weeks will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period, from the randomisation and up to the time point in which an occurrence of a hypoglycaemic episode is considered treatment emergent as offset assuming MAR. The model will include factors for treatment and stratification factor (sub-study, non- sub-study) as categorical factors and baseline HbA<sub>1c</sub> as covariate. The SAS will be used for the analysis.

The results will be described by the rate ratio between treatments and the associated 95% confidence interval and p-value for no treatment difference.

### **Treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemia episodes (yes/no)**

The binary endpoint indicating whether a subject has no treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes or at least one will be analysed using a logistic regression model. The model will include factors for treatment and stratification factor (sub-study, non- sub-study) as categorical factors and baseline HbA<sub>1c</sub> as covariate. The SAS will be used for the analysis.

The results will be described by the odds ratio between treatments and the associated 95% confidence interval and p-value for no treatment difference.

### **Laboratory assessments**

The laboratory assessments supporting the safety objective are change from baseline to week 52 in:

- Haematology
- Biochemistry
- Calcitonin

The above continuous laboratory assessments will be summarised and evaluated by descriptive statistics.

In addition amylase and lipase will be analysed separately using an analysis similar to the primary analysis of the primary endpoint. However this analysis will be based on SAS using the on-treatment observation period.

Both analyses will use the associated baseline and post-baseline responses as covariates instead of HbA<sub>1c</sub>. Lipase and amylase values will be log-transformed prior to the analysis.

## **Pulse**

Change from baseline to week 52 in pulse will be analysed separately with the same model approach as for amylase and lipase but with the pulse value at baseline and post-baseline as covariates instead of HbA<sub>1c</sub>.

## **Categorical safety assessments**

The categorical assessments supporting the safety objective are change from baseline to week 52 in:

- Electrocardiogram (ECG) category
- Physical examination
- Eye examination category

The above assessments will be summarised descriptively

## **17.6 Health economics and/or patient reported outcomes (PROs)**

Change from baseline to week 52 in:

- Scores for selected patient reported outcomes:
  - SF-36v2™ Short Form health survey: Total scores (physical component and mental component) and scores from the 8 domains
  - Diabetes Treatment Satisfaction Questionnaire (DTSQ): Treatment satisfaction score (sum of 6 of 8 items) and the 8 items separately
  - Control of Eating Questionnaire (CoEQ): Scores from the 4 domains and scores from 19 individual items

The PRO questionnaires, SF-36v2™, DTSQ and CoEQ will be used to evaluate the objective regarding Quality of Life. Each of the PRO endpoints will be analysed separately as the other continuous efficacy endpoints for the primary estimand using a similar model approach as for the primary endpoint with the associated baseline and post-baseline responses as covariates.

## 18 Ethics

### 18.1 Benefit-risk assessment of the trial

#### 18.1.1 Risk and precautions

The nonclinical safety programme of semaglutide has not revealed any safety issues precluding use in humans.

The sections below describe the important identified and potential risks and precautions associated with semaglutide treatment. These are based on findings in nonclinical studies and clinical trials with semaglutide as well as other GLP-1RAs. For each of these risks and precautions, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

#### 18.1.2 Identified risk

##### **Gastrointestinal adverse events**

Consistent with findings with other GLP-1RAs, the most frequently reported AEs in clinical trials with semaglutide have been gastrointestinal disorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). Clinical trials have indicated that a low starting dose and gradual dose escalation mitigates the risk of gastrointestinal AEs. Consequently, a low starting dose and dose escalation with 4 week dose-escalation steps have been implemented in the trial.

##### **Diabetic retinopathy complications**

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive anti-diabetic treatment<sup>61-63</sup>. Risk factors for these events include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large improvements in blood glucose may be an additional aggravating factor. Several studies have, however, documented long-term beneficial effects of intensive glycaemic treatment in reducing retinopathy progression<sup>5, 64</sup> even in intensively treated patients who experienced early worsening<sup>62</sup>. In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of events related to diabetic retinopathy in subjects treated with semaglutide compared to placebo. As a precaution in this trial, all subjects are required to have a fundus photography or dilated fundoscopy performed before enrolment into the trial; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded. As part of good diabetes management the investigator is encouraged to ensure adequate monitoring and treatment of diabetic retinopathy in subjects enrolled into the trial<sup>65</sup>.

##### **Cholelithiasis**

Events of gallstones (cholelithiasis) have been reported from clinical trials with semaglutide. These events may lead to hospitalisation and removal of the gallbladder. If cholelithiasis is suspected potential discontinuation of trial product and appropriate clinical follow-up should be considered at the investigator's discretion.

### 18.1.3 Potential risks

#### Medullary thyroid cancer

The human relevance of the proliferative C-cell changes found in rodents treated with GLP-1RAs is unknown, but data suggest that rodents are more sensitive to the mode of action of GLP-1RAs for induction of C-cell tumours. However, as a precaution, subjects with a family or personal history of Multiple Endocrine Neoplasia type 2 (MEN 2) or Medullary thyroid cancer will not be enrolled in the trial. During the trial, calcitonin will be measured at randomisation visit, visit 8 and at V10/V10A, and the guidance for investigators on further evaluation and action on elevated calcitonin concentrations is included in [appendix A](#).

#### Acute pancreatitis

Acute pancreatitis has been reported in subjects treated with GLP-1RAs including semaglutide. As a precaution, subjects with a history of acute or chronic pancreatitis will not be enrolled in the trial. Also, subjects will be informed about the symptoms of acute pancreatitis and serum levels of lipase and amylase will be monitored throughout the trial.

#### Pancreatic cancer

Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from nonclinical studies or clinical trials or post marketing data that GLP-1-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been included as a separate potential risk due to the scientific debate surrounding a potential association to GLP-1-based therapies and the unknown long-term effects of stimulation of  $\beta$ -cells and suppression of  $\alpha$ -cells. Pancreatic cancer has been classified as a potential class risk of GLP-1RAs by EMA.

#### Allergic reactions and injection site reaction

As in the case with all protein-based pharmaceuticals, treatment with semaglutide may evoke allergic reactions. These may include localized injection site reactions or generalized reactions, including urticaria, rash, pruritus as well as anaphylactic reactions. As a precaution, subjects with known or suspected hypersensitivity to trial product(s) or related products will not be enrolled in the trial. In addition, subjects will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the trial product occurs.

#### Hypoglycaemia

Based on current knowledge about the GLP-1RA drug class, there is a risk of hypoglycaemic episodes. Hypoglycaemic episodes have mainly been observed when semaglutide is combined with SU or insulin.

#### Acute kidney injury

In subjects treated with GLP-1RAs, including semaglutide, gastrointestinal AEs such as nausea, vomiting and diarrhoea may lead to significant dehydration and secondary acute kidney injury.

Subjects with gastrointestinal AEs are recommended to drink plenty of fluids to avoid volume depletion. Also, serum creatinine and other markers of kidney function will be monitored throughout the trial.

SGLT-2 inhibitors have also been associated with volume depletion. It is recommended to monitor renal function and for signs and symptoms of fluid loss during therapy. Severe dehydration may be a risk factor for ketoacidosis.

Impaired renal function may increase the risk of metformin associated lactic acidosis when GLP-1RAs are co-administered with metformin. As a precaution, serum creatinine will be measured regularly. In subjects treated with metformin who experience prolonged or severe nausea and vomiting, the investigator should monitor serum creatinine, and if clinically indicated, withhold metformin until resolution of renal dysfunction. The use of the background medication should be in accordance with the current, approved labels.

#### **18.1.4 Other safety considerations**

##### **Teratogenicity (embryo-foetal development toxicity)**

Semaglutide caused embryo-foetal malformations in the rat through a GLP-1 receptor mediated effect on the inverted yolk sac placenta leading to impaired nutrient supply to the developing embryo. Primates do not have an inverted yolk sac placenta which makes this mechanism unlikely to be of relevance to humans. However, as a precaution, females who are pregnant, breast-feeding or intend to become pregnant or are of childbearing potential and not using an adequate contraceptive method will not be enrolled in the trial. In addition, pregnancy tests will be performed at all visits, including screening and follow-up and at any time during the trial if a menstrual period is missed, or as required by local law.

##### **General precautions**

All subjects will be included after a thorough evaluation with regards to in- and exclusion criteria defined in order to ensure that subjects are eligible for trial treatment.

There are also strict glycaemic rescue criteria in place to ensure acceptable glycaemic control during the trial. If rescue medication is required, it should be in accordance with ADA/European Association for the Study of Diabetes<sup>33, 34</sup> (excluding GLP-1RAs, DPP-4 inhibitors, amylin analogues and SGLT-2).

It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2016 Standards of Medical Care in Diabetes<sup>65</sup>.

Further details with regards to safety of trial product are described in the current edition of the IB for semaglutide (NN9535)<sup>25</sup> or any updates thereto or in the current approved label of the relevant SGLT-inhibitors.



## Canagliflozin

Subjects should be considered suitable for treatment with canagliflozin and the use of canagliflozin should be in accordance with the current, approved label. It is important to monitor renal function and for signs and symptoms of volume depletion during therapy. Serum creatinine will be measured regularly for monitoring of renal function.

The most common adverse reactions reported with canagliflozin are female genital mycotic infections, urinary tract infections and increased urination. Other events include hypoglycaemia (with concomitant use of insulin or insulin secretagogues), hypotension, hyperkalemia, increased LDL-C levels and bone fracture. Canagliflozin and other SGLT-2 inhibitors have also been associated with a risk of urinary tract infections and ketoacidosis. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, general malaise and shortness of breath. Ketoacidosis associated with the use of SGLT-2 inhibitors can occur even if blood sugar levels are only relatively elevated or non-elevated. If ketoacidosis is suspected, canagliflozin or canagliflozin placebo should be discontinued and appropriate treatment should be instituted promptly.

A signal of increased risk of lower limb amputations has been associated with the use of canagliflozin and is currently under investigation by the EMA<sup>66</sup> and the FDA<sup>67</sup>. While the review of this risk by the Health Authorities is ongoing, subjects at risk are excluded from participation in this clinical trial and assessment of leg and foot is required at every site visit. The investigators should instruct the subjects enrolled about the importance of regular leg and foot care and to further notify the investigator in case they notice any new pain or tenderness, sores or ulcers, or infections in legs or feet.

### 18.1.5 Benefits

In this trial, subjects will be randomised in a 1:1 manner to one of two treatment arms involving an active add-on treatment regimen anticipated to be more efficacious than the treatment they receive at the time of entry into the trial (metformin only).

Based on the results of the completed clinical trials, semaglutide is expected to provide clinically relevant improvements in glycaemic control and body weight in subjects with type 2 diabetes.

In addition, it is expected that all subjects, will benefit from participation through close contact with the trial site, with close follow-up of their T2D and a careful medical examination, all of which will most likely result in an intensified management of their T2D.

Finally, data from two cardiovascular outcomes trials investigating treatment with GLP-1RAs compared to placebo have indicated that there might be a potential beneficial effect of these drugs on cardiovascular outcomes when added to standard of care in subjects with T2D at high risk of cardiovascular events (see Section [3.1.5.3](#)).

All subjects in this trial will receive trial products and auxiliary supplies free of charge.

## **18.2 Risk and benefit conclusion**

The safety profile for semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of semaglutide in accordance with the planned clinical trial. Completed clinical trials with semaglutide provided clinically relevant improvements in glycaemic control and body weight.

Safety and efficacy will be monitored regularly and acceptable glycaemic control will be reinforced at all times during the trial.

In conclusion, the potential risk to the subjects in this trial is considered low and acceptable in view of the anticipated benefits semaglutide would provide to patients with T2D.

## **18.3 Informed consent**

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP<sup>2</sup> and the requirements in the Declaration of Helsinki<sup>3</sup>.

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand.

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the investigator must inform the subject in a timely manner, and a revised written subject information must be provided and a new informed consent must be obtained.

In order to avoid missing data, the subjects will be informed about the importance of completing the trial also if the subjects discontinue treatment with trial product.

#### **18.4 Data handling**

If the subject withdraws from the trial or is lost to follow up, then the subject's data will be handled as follows:

- Data already collected and any data collected at the end-of-trial visit including follow up visits will be retained by Novo Nordisk, entered into the database and used for the clinical trial report.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

#### **18.5 Information to subjects during trial**

All written information to subjects must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

#### **18.6 Premature termination of the trial and/or trial site**

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If the trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have participated in the trial. If it has an impact, the actions needed to inform and protect the subjects should be described.

## 19 Protocol compliance

### 19.1 Protocol deviations

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF.

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

### 19.2 Prevention of missing data

The importance of subject retention will be addressed by Novo Nordisk in the training and communication with the trial sites.

The subjects will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial.

Close surveillance of subject retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal of consent to secure early mitigations in collaboration with the trial sites.

The investigator will make every effort to ensure that all assessments are performed and data is collected. If missing data does occur the reason will be collected via the protocol deviation process, see Section [19.1](#). Novo Nordisk will monitor protocol deviations on an on-going basis throughout the trial followed by appropriate actions (e.g. re-training of site staff).

## 20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

## 21 Critical documents

Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure SmPC or similar labelling
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

### **Only applicable for US trial sites:**

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

### **FDA form 1572:**

For US sites:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

Protocol  
Trial ID:NN9535-4270  
UTN:U1111-1180-3651  
EudraCT no.:2016-000989-35

~~CONFIDENTIAL~~

Date: 19 December 2016  
Version: 3.0  
Status: Final  
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**Novo Nordisk**

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP<sup>2</sup> applicable regulatory requirements and the Declaration of Helsinki<sup>3</sup>.

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

## 22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the trial site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator will follow instructions from Novo Nordisk when processing data.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents including the subject identification code list must be kept in a secure locked facility, so no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

## 23 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial.

One or two investigators will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications<sup>66</sup>.

### 23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure<sup>35</sup>.

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.



In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

Where required by the journal, the investigator from each trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

#### **23.1.1 Authorship**

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors<sup>66</sup> (sometimes referred to as the Vancouver Criteria).

Novo Nordisk will appoint investigator(s) to prepare publications in collaboration with Novo Nordisk.

#### **23.1.2 Site-specific publication(s) by investigator(s)**

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

#### **23.2 Investigator access to data and review of results**

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

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Individual investigators will have their own research subjects' data, and will be provided with the randomisation code after results are available.

## 24 Retention of clinical trial documentation

### 24.1 Retention of clinical trial documentation

Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

The files from the trial site/institution must be retained for 15 years after end of trial as defined in section [7](#), or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

## **25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities**

### **IRB/IEC:**

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

### **Regulatory Authorities:**

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

## 26 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence, or any other liability of the sites or investigators conducting the trial, or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with:

For Mexico only:

- a) *Novo Nordisk carries product liability for its products assumed under the special laws, acts/and/or guidelines for conducting trials in any country, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance.*
- b) *If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the trial medication and/or a trial procedure that otherwise would not have been part of his/her regular care, the subject will receive from the Institution or Medical Care Establishment and free of charge, the appropriate medical treatment as required.*
- c) *In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the trial sponsor in accordance with the terms provided by all applicable regulations; even if the subject discontinues his/her participation in the trial by his own will or by a decision from the investigator.*
- d) *By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.*

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## **Statistical Analysis Plan**

**Trial ID: NN9535-4270**

**SUSTAIN 8 – semaglutide versus canagliflozin**

**Efficacy and safety of semaglutide versus canagliflozin as add-on to metformin in subjects with type 2 diabetes**

Nanna Leonora Lausvig  
Biostatistics Semaglutide s.c.

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## List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
BG	blood glucose
BMI	body mass index
CoEQ	Control of Eating Questionnaire
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DXA	DXA analysis set / dual X-ray absorptiometry
ECG	electrocardiogram
FAS	full analysis set
FPG	fasting plasma glucose
HbA <sub>1c</sub>	glycosylated haemoglobin
HDL	high-density lipoprotein
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
OW	once weekly
PP	per protocol
PRO	patient reported outcome
PT	preferred term
SAS	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SE	standard errors
SF-36v2 <sup>TM</sup>	Short form healthy survey
SMPG	self-measured plasma glucose
SUSTAIN	Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes
T2D	type 2 diabetes
TEAE	treatment emergent adverse events

# 1 Introduction

## 1.1 Trial information

This is a 52-week, confirmatory, randomised, double-blind, double dummy, active-controlled, multicentre, multinational, two-arm, parallel-group trial.

### Primary objective

To compare the effect of once-weekly (OW) dosing of subcutaneous semaglutide (1.0 mg) versus once-daily dosing of oral canagliflozin (300 mg) on glycaemic control in subjects with type 2 diabetes (T2D) on a background treatment of metformin.

### Secondary objectives

To compare the effects of semaglutide s.c. 1.0 mg once-weekly versus canagliflozin 300 mg once daily after 52 weeks of treatment in subjects with T2D with regards to:

- Weight management
- Other parameters of effect, safety and Patient Reported Outcomes

See the protocol for trial NN9535-4270 for further details.

## 1.2 Scope of the statistical analysis plan

This SAP is based on the protocol “SUSTAIN 8 – semaglutide versus canagliflozin, Efficacy and safety of semaglutide versus canagliflozin as add-on to metformin in subjects with type 2 diabetes”, version 3.0.

# 2 Statistical considerations

## 2.1 General considerations

No interim analyses or other analyses of un-blinded or between group data will be performed before the database is locked.

Laboratory values below the lower limit of quantification (LLOQ) will be set to  $\frac{1}{2}$ LLOQ.

Results from a statistical analysis will be presented by the estimated treatment contrasts at week 52 with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference if not otherwise specified.

The comparison presented from a statistical analysis will be semaglutide 1.0 mg versus canagliflozin 300 mg

If no statistical analysis is specified, data will be presented using relevant summary statistics.

Data from all trial sites will be analysed and reported together.

The regions used in the statistical analyses are defined as:

- North America (United States and Canada)
- Region Europe (United Kingdom, Ireland and Sweden)
- International Operations (Lebanon, Malaysia, Argentina, Mexico, Brazil, India)

### 2.1.1 Data transformations

A number of the continuous parameters will be log-transformed prior to statistical analysis. The output tables and figures will show the results of the analysis back-transformed to the original scale, implying that log-treatment-differences are reported as treatment ratios. Confidence intervals for the treatment ratios will be calculated as exponentiated upper and lower limits for log-treatment difference confidence intervals. The standard errors (SE) of the back-transformed mean and ratio to baseline estimates are also provided; these SEs are calculated using the delta-method (first order Taylor approximation), whereby the SE on the original scale is calculated as the product of the SE on log-scale and the exponentiated estimate of the mean (geometric mean).

### 2.1.2 Definition of baseline

For each assessment, the baseline assessment is defined as the latest available measurement at or prior to the randomisation visit. This specifically implies that if a visit 2 assessment is missing (whether it was planned or not planned) then the screening assessment (from visit 1), if available, will be used as the baseline assessment.

### 2.1.3 Primary estimand

To further detail the trial objective an estimand is defined which is a *de-jure* (efficacy) estimand:

Primary estimand

- The treatment difference between semaglutide and canagliflozin at week 52 for all randomised subjects if all subjects completed treatment and did not initiate rescue medication

This primary *de-jure* estimand is considered clinically relevant as it assesses the glycaemic benefit a person with T2D is expected to achieve if initiating and continuing treatment with semaglutide compared to canagliflozin. Accordingly, only data collected prior to discontinuation of trial product or initiation of rescue medication will be used to draw inference. This will avoid confounding from rescue medication.

### 2.1.4 Trial completion

Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial. The full duration of the trial is defined as up to and including the follow-up visit (P11). Subjects completing the follow-up visit (P11) will be considered trial completers.

### 2.1.5 Missing data considerations at week 52

The actual rate of missing data at week 52 is expected to be maximum 10% based on the rate of trial completers from the subcutaneous semaglutide phase 3a clinical development programme. The frequency of missing data is expected to be similar in the semaglutide and the canagliflozin groups.

When estimating the primary estimand, the combined rate of missing data, subjects discontinuing treatment prematurely or initiating rescue medication on top of trial product, is expected to be maximum 30%. This is based on the results from the subcutaneous semaglutide phase 3a clinical development program. Based on these data, premature treatment discontinuation due to gastrointestinal adverse events (AEs) is expected to be low but more frequent in semaglutide compared to canagliflozin. Other reasons for discontinuing treatment are assumed to be unrelated to treatment and therefore occur with similar rates, so overall the frequency of missing data or data not used at week 52 in the primary analysis is expected to be slightly larger in semaglutide as compared to canagliflozin.

To document the extent and reason(s) for missing data, descriptive summaries and graphical representation of extent, reason(s) for and pattern of missing data will be presented by treatment group.

## 2.2 Sample size calculation

The primary endpoint, change from baseline to week 52 in HbA<sub>1c</sub> (%-point) will be tested for non-inferiority and superiority of semaglutide vs. canagliflozin. The confirmatory secondary endpoints, change from baseline to week 52 in body weight (kg) and change from baseline to week 52 in total fat mass (kg) are planned to be tested for superiority of semaglutide vs. canagliflozin.

The sample size calculation is made to ensure a power of at least 90% for meeting HbA<sub>1c</sub> superiority of semaglutide vs. canagliflozin out of the four pre-specified confirmatory hypotheses shown in [Table 2-2](#). The closed testing procedure described in Bretz et.al. 2011<sup>1</sup> combined with a hierarchical approach is used to control the overall type-1 error at a two-sided 5% level. The statistical testing strategy is built on the following principle:

- Glycaemic efficacy must be established by HbA<sub>1c</sub> non-inferiority before testing for added benefits in terms of superiority in terms of HbA<sub>1c</sub> or body weight.
- HbA<sub>1c</sub> and body weight superiority must be established before testing for added benefits in terms of superiority in terms of total fat mass.

The sample size is calculated using the calcPower function in the R package, gMCP<sup>2</sup> using 10,000 simulations. All of the four pre-specified confirmatory tests are assumed to be independent. Since



some of these tests are positively correlated, the assumption of independence is viewed as conservative. The four hypotheses are:

- HbA<sub>1c</sub> non-inferiority of semaglutide 1.0 mg vs. canagliflozin 300 mg with a non-inferiority margin of 0.3
- HbA<sub>1c</sub> superiority of semaglutide 1.0 mg vs. canagliflozin 300 mg
- Body weight superiority of semaglutide 1.0 mg vs. canagliflozin 300 mg
- Total fat mass superiority of semaglutide 1.0 mg vs. canagliflozin 300 mg

The sample size assumptions for efficacy based on on-treatment data without rescue medication, a treatment effect based on in-trial data (see Section 2.3.1) and the standard deviations (SD) are given in Table 2-1. The HbA<sub>1c</sub> and body weight assumptions are based on the efficacy results and an observed reduction of approximately 20% and 15% respectively in in-trial treatment effect compared to efficacy in the subcutaneous semaglutide phase 3a clinical development programme.<sup>4-7</sup>

A similar reduction in the in-trial treatment effect compared to efficacy is assumed with canagliflozin as comparator. The total fat mass assumption is based on the relevant literature focusing on fat mass<sup>8-10</sup>, which indicates a smaller SD for total fat mass as compared to body weight.

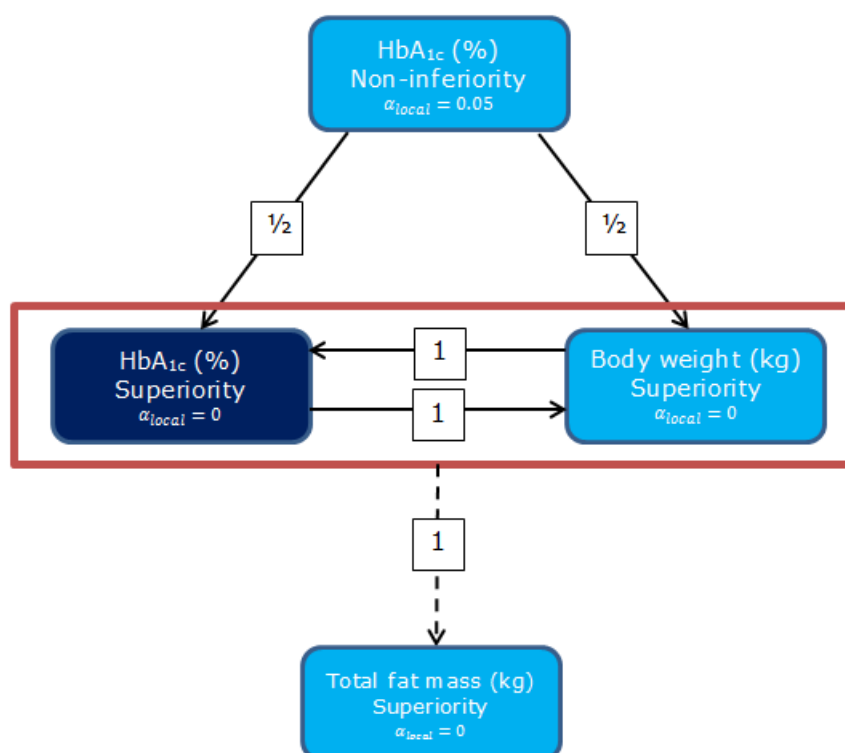
**Table 2-1 Assumptions used in the sample size calculation**

Semaglutide vs. canagliflozin	HbA <sub>1c</sub> (%-points)	Body weight (kg)	Total fat mass (kg)
Efficacy	-0.32	-2.4	-1.8
In-trial treatment effect	-0.256	-2.04	-1.53
Standard deviation	1.1	4.0	3.5

With the above assumptions, allocating 392 subjects to the semaglutide arm and the canagliflozin arm provides 90% power to confirm HbA<sub>1c</sub> superiority of semaglutide vs. canagliflozin across plausible assumptions.

**Table 2-2 Calculated powers for meeting individual hypotheses**

Statistical test	HbA <sub>1c</sub> non-inferiority	HbA <sub>1c</sub> superiority	Body weight superiority	Total fat mass superiority
Efficacy Power (%)	>99%	90%	>99%	91%
In-trial effect power (%)	>99%	90%	>99%	74%



The overall significance level of  $\alpha = 0.05$  (two-sided) is initially allocated to the HbA<sub>1c</sub> non-inferiority test. The local significance level ( $\alpha$ -local) will be reallocated if a hypothesis is confirmed according to the weight given by the directed edges between nodes (hypotheses). The total fat mass superiority test will receive the overall significance of  $\alpha = 0.05$  (two-sided) if and only if both HbA<sub>1c</sub> and body weight superiority are confirmed at their respective local significance levels.

**Figure 2-1 Graphical illustration of the closed testing procedure**

The overall significance level of  $\alpha = 0.05$  (two-sided) is initially allocated to the HbA<sub>1c</sub> non-inferiority test. The local significance level ( $\alpha$ -local) will be reallocated if a hypothesis is confirmed according to the weight given by the directed edges between nodes (hypotheses). The total fat mass superiority test will receive the overall significance of  $\alpha = 0.05$  (two-sided) if and only if both HbA<sub>1c</sub> and body weight superiority are confirmed at their respective local significance levels.

### 2.2.1 Sample size for the sub-study (dual X-ray absorptiometry)

For the sub-study on body composition assuming an efficacy treatment difference of 1.8 kg and a SD of 3.5 kg, 174 subjects (87 subjects in each arm) will provide 92% power to establish a statistical significant difference resulting in 91% power for confirming superiority in the testing strategy in terms of fat mass loss (kg) at week 52 using a two-sided significance level of 5%.

### 2.3 Definition of analysis sets

The following analysis sets will be defined:

**Full analysis set (FAS):** includes all randomised subjects. Subjects in the FAS will contribute to evaluation “as randomised”.

**DXA analysis set:** includes all subjects in FAS who are included in the DXA sub-study. Subjects in the DXA analysis set will contribute to the evaluation “as randomised”.

**Safety analysis set (SAS):** includes all subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation based on the trial product received for the majority of the period they were on treatment. This will be referred to as contributing to the evaluation “as treated”.

**Per protocol (PP) analysis set:** includes all subjects in the FAS who fulfil the following criteria:

- Have not violated any inclusion criteria
- Have not fulfilled any exclusion criteria
- Have a non-missing HbA<sub>1c</sub> measurement at screening and/or randomisation
- Is on trial product at visit 8 and have at least one non-missing HbA<sub>1c</sub> measurement at or after visit 8.

Subjects in the PP analysis set will contribute to the analysis “as treated” as defined for the SAS.

### 2.3.1 Data selections and observation periods

Subjects and data to be used in an analysis will be selected in a two-step manner.

- Firstly, subjects will be selected based on the specified analysis set
- Secondly, data points on the selected subjects from first step will be selected based on the specified observation period

#### Definition of the observation periods

**In-trial:** This observation period represents the time period where subjects are considered to be in the trial after randomisation, regardless of discontinuation of trial product or initiation of rescue medication. The in-trial observation period starts at randomisation (as registered in IWRS) and ends at the date of:

- The last direct subject-site contact, which is scheduled to take place 5 weeks after planned last dose of trial product at a follow-up visit
- Withdrawal for subjects who withdraw their informed consent
- The last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up
- Death for subjects who dies before any of the above

For subjects not randomised but exposed to trial product the in-trial period starts at the date of first dose of trial product

For DXA assessments the last direct subject-site contact is defined as the date of the last collected data for the subject.

**On-treatment:** This observation period represents the time period where subjects are considered treated with trial product. The observation period is a sub-set of the in-trial observation period. It starts at the date of first dose of trial product. Two slightly different end dates will be needed to cover all assessments appropriately according to the flow chart. For adjudicated events, electrocardiograms (ECGs) and AEs including hypoglycaemic episodes, the observation period ends at the first date of any of the following:

- the follow-up visit (P11)
- the follow-up prematurely discontinuation visit (P11A)
- the last date on trial product + 42 days
- the end-date for the in-trial observation period

The follow-up visit is scheduled to take place 5 weeks after the last date on trial product corresponding to approximately five half-lives of subcutaneous semaglutide. The visit window for the follow-up visit is + 7 days, which is the reason for the 42 days specified in the bullet above. Hence, for those assessments this period reflects the period in which subjects are exposed.

For efficacy and other safety assessments (laboratory assessments, physical examination and vital signs) the observation period ends at the last date on trial product + 7 days. This ascertainment window corresponds to the dosing interval and will be used to avoid attenuation of a potential treatment effect on endpoints for which the effect is reversible shortly after treatment discontinuation. Hence, for those assessments this period reflects the period in which subjects are treated.

**On-treatment without rescue medication:** This observation period is a sub-set of the on-treatment observation period, where subjects are considered treated with trial product, but have not initiated any rescue medications. Specifically it starts at date of first dose of trial product and the observation period ends at the first date of any of the following:

- the last dose of trial product +7 days
- initiation of rescue medication

The 'on-treatment without rescue medication' observation period will be the primary observation period for efficacy evaluations. The in-trial observation period will be considered supportive for efficacy evaluation. Safety will be evaluated based on the in-trial and the on-treatment observation periods unless otherwise specified.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period. For adjudicated events, the onset date will be the EAC adjudicated onset date.

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion will be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

## 2.4 Primary endpoint

The primary endpoint is change from baseline to week 52 in HbA<sub>1c</sub>.

### 2.4.1 Primary analysis for the primary estimand

The primary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 52 from the 'on-treatment without rescue medication' observation period. Imputation of missing data will be handled using multiple imputation assuming that missing data is missing at random (MAR). Missing data will be imputed using observed data within the same group defined by the randomised treatment (semaglutide/canagliflozin). It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who receive the same treatment.

Technically missing values will be imputed as follows:

- Intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each of the treatment groups separately and 500 copies of the dataset will be generated
- A sequential regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and sequentially continuing to the last planned visit at week 52. A model used to impute missing values at each planned visit will be fitted for each of the treatment groups using observed data. The model will include stratification factor (sub-study, non-sub-study) and region as categorical effects and baseline and post-baseline HbA<sub>1c</sub> values observed or imputed prior to the visit in question as covariates.
- An ANCOVA with treatment, stratification factor (sub-study, non-sub-study) and region as categorical effects and baseline HbA<sub>1c</sub> as a covariate will be used to analyse HbA<sub>1c</sub> values at week 52 for each of the 500 complete data sets generated as part of the imputation of missing values. Rubin's rule will be used to combine the analysis results in order to draw inference.

From this analysis, the estimated treatment difference between semaglutide and canagliflozin at week 52 will be presented together with the associated two-sided 95% confidence interval and unadjusted two sided p-values for testing non-inferiority and superiority.

## 2.4.2 Primary hypotheses

For the primary HbA<sub>1c</sub> endpoint the following confirmatory one-sided hypotheses are planned to be tested for semaglutide versus canagliflozin. Let the mean treatment difference be defined as  $\mu =$  (semaglutide minus canagliflozin):

- Non-inferiority, using a non-inferiority margin of 0.3%-point
  - H<sub>0</sub>:  $\mu \geq 0.3\%$ -point against H<sub>a</sub>:  $\mu < 0.3\%$ -point
- Superiority
  - H<sub>0</sub>:  $\mu \geq 0.0\%$ -point against H<sub>a</sub>:  $\mu < 0.0\%$ -point

Operationally the hypotheses will be evaluated by two-sided tests.

The non-inferiority margin of 0.3 is chosen based on the diabetes guideline<sup>11, 12</sup> and the effect of canagliflozin on glycaemic effect seen in a similar trial (DIA3006<sup>3</sup>) where canagliflozin was used as add on to metformin. In this trial canagliflozin showed an HbA<sub>1c</sub> treatment difference to placebo of -0.77%-point. Hence, based on this trial, the chosen margin of 0.3 provides assurance that semaglutide has an effect compared to placebo greater than 0 with a clinically relevant size. With regards to the constancy assumption, controlled clinical trials have consistently established that canagliflozin is an effective anti-diabetic drug. Therefore, lack of trial sensitivity with canagliflozin as comparator is not anticipated to be an issue in this trial.

## 2.4.3 Multiplicity and criteria for confirming hypotheses

The Type-I error for testing the four confirmatory hypotheses related to the HbA<sub>1c</sub>, body weight, and fat mass endpoints will be preserved in the strong sense at 5% (two-sided) using the weighted Bonferroni-based closed testing procedure described in Bretz et. al.<sup>1</sup> and outlined in [Figure 2-1](#). The first hypothesis to be tested is non-inferiority of HbA<sub>1c</sub>. It will be tested at the overall significance level (5%) while allocating 0% local significance level to the remaining three hypotheses. For this hypothesis, and in general, if a hypothesis is confirmed the significance level will be reallocated according to the weight and the direction of the edges going from the confirmed hypothesis to the next hypotheses as specified in [Figure 2-1](#). Total fat mass will be tested at the overall significance level if each of the other 3 hypotheses is confirmed, otherwise its local significance level will remain 0%. Each of the following hypotheses will be tested at their local significance level ( $\alpha$ -local). This process will be repeated until no further hypotheses can be confirmed.

Non-inferiority and subsequent superiority will be considered confirmed if the mean treatment difference is supporting the corresponding alternative hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below its local two-sided significance level as defined by the closed testing procedure in [Figure 2-1](#). This is equivalent to using a one-sided p-value (nominal  $\alpha = 0.025$ ) and a one-sided 2.5% overall significance level in the closed testing procedure.

## 2.4.4 Statistical subgroup analyses of HbA<sub>1c</sub>

Five subgroups based on baseline HbA<sub>1c</sub> values are defined as follows:

1.  $\leq 7.5\%$
2.  $> 7.5\%$  to  $8.0\%$  (inclusive)
3.  $> 8.0\%$  to  $8.5\%$  (inclusive)
4.  $> 8.5\%$  to  $9.0\%$  (inclusive)
5.  $> 9.0\%$

Change from baseline in HbA<sub>1c</sub> at week 52 for subgroups based on baseline HbA<sub>1c</sub> values will be analysed for the primary estimand using a similar multiple imputation approach as described in section [2.4.1](#). The complete data sets from the primary analysis will be reused. However the ANCOVA model used to analyse the 500 complete data sets will additionally include the interaction effect of subgroup and treatment as a categorical effect. Rubin's rule will then be used to combine the results and the p-value for the interaction effect and estimated treatment differences at 52 weeks with corresponding two-sided 95% confidence intervals for each subgroup will be presented.

#### **2.4.5 Sensitivity analyses**

In order to investigate the robustness of the conclusions from the primary analysis and to stress test the MAR assumption for missing data tipping point sensitivity analyses will be performed for the primary estimand both for the sensitivity of the non-inferiority and the superiority HbA<sub>1c</sub> hypotheses.

##### **2.4.5.1 Sensitivity analyses for the primary estimand**

The estimation of the primary estimand will be repeated using the following sensitivity analysis:

- Tipping-point analysis (pattern mixture model based) based on the FAS using the 'on-treatment without rescue medication' observation period. In this analysis, subjects from the semaglutide group with missing observations will be given a penalty, i.e., it is assumed that subjects with missing observations who are randomised to semaglutide will receive a treatment that is worse than subjects with observed values who are randomised to semaglutide. The idea is to gradually increase the penalty to evaluate at which level the superiority conclusion of the analyses in terms of statistical significance is changed. The tipping point is the penalty level, at which the magnitude of efficacy reduction in subjects with missing data creates a shift in the treatment effect of semaglutide from being statistically significantly better than canagliflozin to being non-statistically significantly better for the superiority test and similarly for the non-inferiority test. Technically, this analysis will be implemented by replicating the primary analysis including the assumption of MAR but subsequently adding increasing penalty values at week 52 to imputed observations in the semaglutide group before applying ANCOVA on the 500 complete data sets.

##### **2.4.5.2 Other sensitivity analyses**

The following additional sensitivity analyses are specified:

- Retrieved drop-out analysis based on the FAS using post-baseline measurements up to and including week 52 from the in-trial observation period. Missing data will be imputed using the same approach as described for the primary analysis of the primary estimand. However the imputation will be done within the same group defined not only by the randomised treatment (semaglutide/canagliflozin) but also by the status of treatment completion (still on randomised treatment at week 52 yes/no) (4 groups in total). It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who at week 52 are similar in terms of randomised treatment and treatment completion status. In addition in the imputation step stratification factor and region is not included in the model in order to avoid potential issues with sparse data. This analysis could be considered addressing an effectiveness estimand. The retrieved drop-out is carried out for the superiority testing only.
- PP analysis based on the PP data set using the ‘on-treatment without rescue’ observation period. This analysis will be carried out for non-inferiority testing only. The statistical analysis will be the same as the primary analysis for the primary estimand.

## 2.5 Secondary endpoints

### 2.5.1 Confirmatory secondary endpoints

Change from baseline to week 52 in body weight (kg) and change from baseline to week 52 in total fat mass (kg) will be confirmatory secondary endpoints.

The primary estimand will be estimated using the same approach as described for the primary HbA<sub>1c</sub> endpoint. Body weight and total fat mass will be tested for superiority. Baseline and post-baseline body weight will be used as covariates instead of HbA<sub>1c</sub> for the analysis of body weight. The analysis of total fat mass will be based on the DXA analysis set, stratification factor will not be included in the model and baseline fat mass will be used as covariate instead of baseline HbA<sub>1c</sub>. Since only baseline and end-of-treatment DXA scans are performed, the missing data pattern will be monotone by default. As a consequence MCMC-imputation is not needed and no post-baseline data will be included as covariates in the imputation model. Superiority will be considered confirmed if the mean treatment difference is supporting the corresponding hypothesis and the two-sided p-value from the primary analysis of the primary estimand is strictly below its local two-sided significance level resulting from the closed testing procedure in [Figure 2-1](#).

The tipping point sensitivity analysis pre-specified to evaluate the robustness of the conclusions from the primary analysis of HbA<sub>1c</sub> will also be performed to evaluate the robustness of the conclusions from the body weight and total fat mass superiority tests. The analyses will be based on FAS and the DXA analysis set respectively. In addition, the retrieved drop-out sensitivity analysis will also be performed for body weight. For total fat mass, the data collection does not support a retrieved drop-out analysis as there are no systematic data collection at visit 10 for subjects



discontinuing treatment prematurely. Therefore, a supplementary in-trial analysis will be performed in which the imputation is done within the same group defined by randomised treatment only. The observation period for this analysis is the in-trial period. Besides this, the imputation procedure follows that of the confirmatory analysis for total fat mass, i.e. region is included in the imputation model and no MCMC imputation is performed.

## **2.5.2 Supportive secondary endpoints**

No sensitivity analyses are planned for the supportive secondary endpoints.

### **2.5.2.1 Efficacy endpoints**

#### **Continuous endpoints**

The continuous endpoints are change from baseline to week 52 in:

- Fasting plasma glucose (FPG)
- Self-measured plasma glucose (SMPG), 7-point profile:
  - Mean 7-point profile
  - Mean post prandial increment (over all meals)
- Fasting blood lipids (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides)
- Body mass index (BMI) and waist circumference
- Systolic and diastolic blood pressure
- Body weight (%)
- Total fat mass (%-point)
- Total lean mass (kg)
- Total lean mass (%-point)
- Visceral fat mass (kg)
- Visceral fat mass (%-point)
- Ratio between total fat mass and total lean mass

The above continuous endpoints will be analysed for the primary estimand separately using a similar model approach as for the primary endpoint with the associated baseline and post-baseline responses as covariates instead of HbA<sub>1c</sub> for their respective analyses. The DXA endpoints (total fat mass, total lean mass, visceral fat mass and ratio between total fat mass and total lean mass) will be analysed using a similar approach as for the confirmatory secondary endpoint, total fat mass (kg), with the associated baseline values as covariate instead of total fat mass (kg).

Fasting lipid profile endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

#### **Mean 7-point profile self-measured plasma glucose definition**

Subjects will be asked to perform SMPG measurements before and 90 minutes after breakfast, lunch, dinner, and at bedtime.

Mean of the 7-point profile is defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time.

## Binary endpoints

The binary endpoints are subjects who after 52 weeks treatment achieve (yes/no):

- $\text{HbA}_{1c} < 7.0\%$  (53 mmol/mol), American Diabetes Association (ADA) target
- $\text{HbA}_{1c} \leq 6.5\%$  (48 mmol/mol), American Association of Clinical Endocrinologists (AACE) target
- Weight loss  $\geq 3\%$
- Weight loss  $\geq 5\%$
- Weight loss  $\geq 10\%$
- $\text{HbA}_{1c} < 7.0\%$  (53 mmol/mol) without severe or blood glucose confirmed symptomatic hypoglycaemia episodes and no weight gain
- $\text{HbA}_{1c}$  reduction  $\geq 1\%$ -point
- $\text{HbA}_{1c}$  reduction  $\geq 1\%$ -point and weight loss  $\geq 3\%$
- $\text{HbA}_{1c}$  reduction  $\geq 1\%$ -point and weight loss  $\geq 5\%$
- $\text{HbA}_{1c}$  reduction  $\geq 1\%$ -point and weight loss  $\geq 10\%$

The above 10 endpoints will be analysed for the primary estimand. The analyses for the primary estimand for all 10 endpoints will be based on the 'on-treatment without rescue medication' observation period. They will be analysed separately using the same type of logistic regression model with treatment, stratification factor (sub-study, non- sub-study), region and associated baseline and post-baseline response(s) (i.e.  $\text{HbA}_{1c}$  responses for  $\text{HbA}_{1c}$  endpoints, body weight responses for weight endpoints and both  $\text{HbA}_{1c}$  and body weight responses for the binary endpoints that combine both parameters) as covariates. To account for missing data, the analysis will be made using a sequential multiple imputation approach as described below:

- The binary endpoint will be derived based on the 500 complete data sets from the primary analysis of  $\text{HbA}_{1c}$  and the confirmatory analysis of body weight.
- Each of the created complete data sets will be analysed with the logistic regression model. Estimated odds ratios will be log transformed and inference will be drawn using Rubin's rule.<sup>13</sup>

The results after applying Rubin's rule will be back-transformed and described by the odds ratio between treatments and the associated 95% confidence interval and p-value for no treatment difference.

### 2.5.2.2 Safety endpoints

The safety endpoints will be evaluated based on SAS using the on-treatment observation period and the in-trial observation period unless otherwise stated.

## Adverse Events

The following endpoint related to AEs is used to support the safety objective;

- Number of treatment emergent adverse events (TEAEs)

A treatment-emergent AE is an event that has onset date (or increase in severity) during the on-treatment observation period. These will therefore be referred to as ‘on-treatment AEs’ hereafter. On-treatment AEs are summarised descriptively in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). These summaries are replicated by outputs including all ‘in-trial’ AEs (i.e., AEs with onset date [or increase in severity] during the ‘in-trial’ observation period). AEs with onset after the end of the ‘in-trial’ observation period will be reported in a listing. The development over time in gastrointestinal AEs will be presented graphically.

The most frequent AEs will be defined as preferred terms (PTs) that are experienced by at least 5% of the subjects in any of the treatment arms.

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

### **Hypoglycaemic episodes**

The following two endpoints related to hypoglycaemic episodes are used to support the safety objective:

- Number of treatment-emergent severe or blood glucose (BG)-confirmed symptomatic hypoglycaemic episodes
- Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes (yes/no)

Data on treatment-emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one episode, the percentage of subjects with at least one episode (%), the total number of episodes and the episode rate per 100 years of exposure. Summaries of treatment-emergent hypoglycaemic episodes will be presented as an overview including all episodes and episodes by severity.

### **Classification of Hypoglycaemia:**

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset is in the on-treatment period (see definition of observation period in section [2.3.1](#))

Nocturnal hypoglycaemic episodes: are episodes occurring between 00:01 and 05.59 both inclusive.

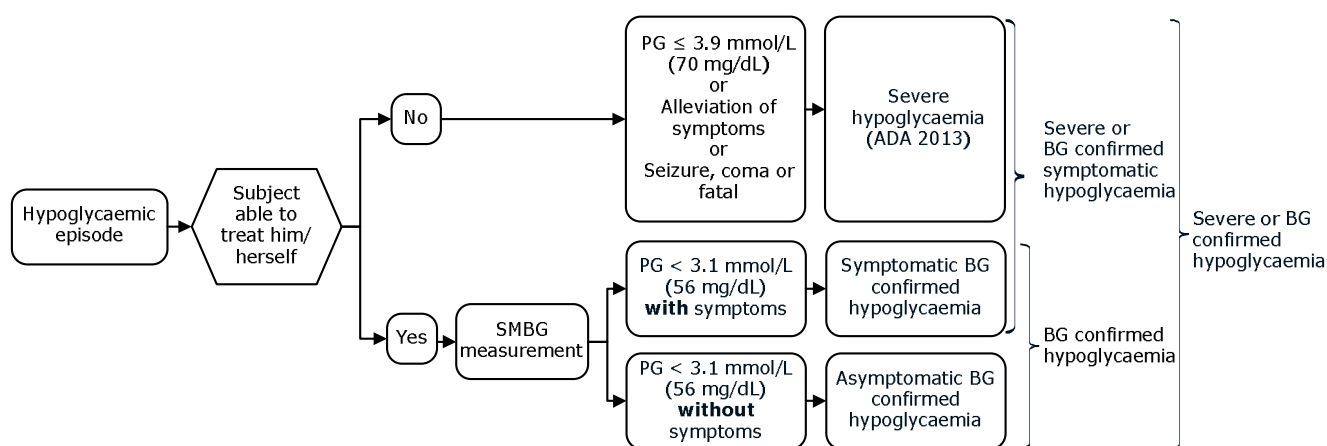
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see [Figure 2-2](#)) and the ADA classification of hypoglycaemia (see [Figure 2-3](#)).

### **Novo Nordisk classification of hypoglycaemia**

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL).<sup>14</sup> Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see [Figure 2-2](#)) in addition to the ADA classification:

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification<sup>15</sup> or BG confirmed by a plasma glucose value  $<3.1$  mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.



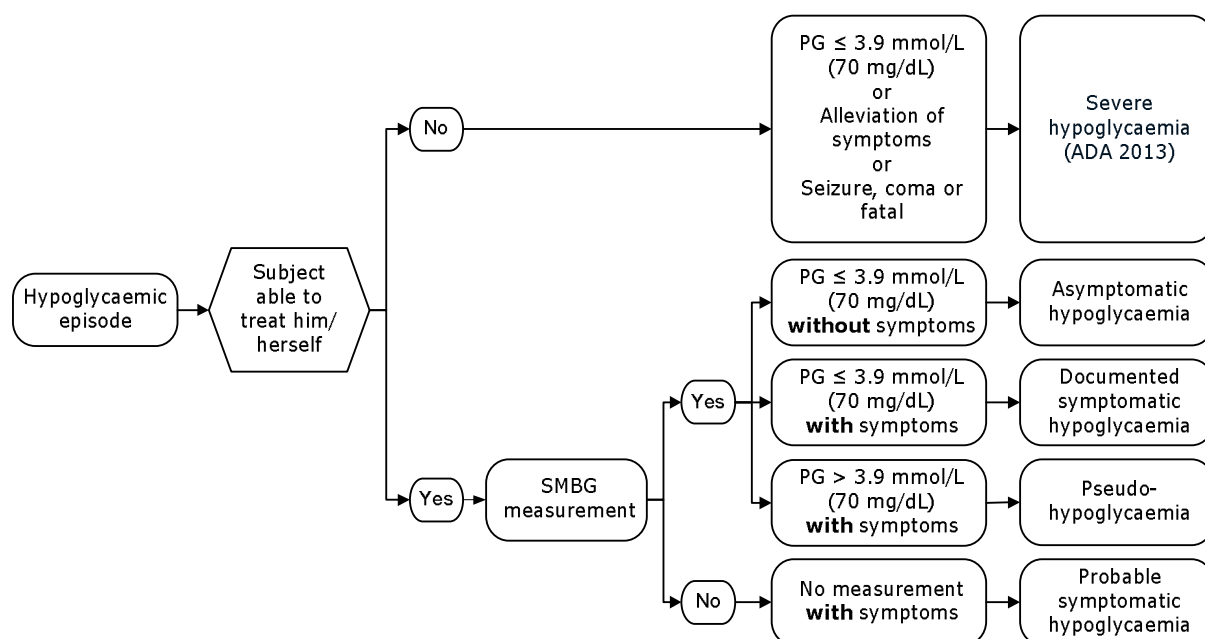
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

**Figure 2-2 Novo Nordisk classification of hypoglycaemia**

### American Diabetes Association classification<sup>15</sup> of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration  $>3.9$  mmol/L (70 mg/dL) but approaching that level.

- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL).



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

**Figure 2-3 American Diabetes Association classification of hypoglycaemia**

### Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes

Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 56 weeks will be analysed using a negative binomial regression model with a log -link function and the logarithm of the time period, from the randomisation and up to the time point in which an occurrence of a hypoglycaemic episode is considered treatment emergent as offset assuming MAR. The model will include factors for treatment and stratification factor (sub-study, non- sub-study) as categorical factors and baseline HbA<sub>1c</sub> as covariate. The SAS will be used for the analysis.

The results will be described by the rate ratio between treatments and the associated 95% confidence interval and p-value for no treatment difference.

### **Treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemia episodes (yes/no)**

The binary endpoint indicating whether a subject has no treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes or at least one will be analysed using a logistic regression model. The model will include factors for treatment and stratification factor (sub-study, non- sub-study) as categorical factors and baseline HbA<sub>1c</sub> as covariate. The SAS will be used for the analysis.

The results will be described by the odds ratio between treatments and the associated 95% confidence interval and p-value for no treatment difference.

### **Laboratory assessments**

The laboratory assessments supporting the safety objective are change from baseline to week 52 in:

- Haematology
- Biochemistry
- Calcitonin

The above continuous laboratory assessments will be summarised and evaluated by descriptive statistics.

In addition amylase and lipase will be analysed separately using an analysis similar to the primary analysis of the primary endpoint. However this analysis will be based on SAS using the on-treatment observation period.

Both analyses will use the associated log-transformed baseline and post-baseline responses as covariates instead of HbA<sub>1c</sub>. Lipase and amylase values will be log-transformed prior to the analysis.

### **Pulse**

Change from baseline to week 52 in pulse will be analysed separately with the same model approach as for amylase and lipase but with the pulse value (not log-transformed) at baseline and post-baseline as covariates instead of HbA<sub>1c</sub>.

## Categorical safety assessments

The categorical assessments supporting the safety objective are change from baseline to week 52 in:

- ECG category
- Physical examination
- Eye examination category

The above assessments will be summarised descriptively

## 2.6 Health economics and/or patient reported outcomes

Change from baseline to week 52 in scores for selected PROs:

- SF-36v2™ Short Form health survey: Total scores (physical component and mental component) and scores from the 8 domains
- Diabetes Treatment Satisfaction Questionnaire (DTSQ): Treatment satisfaction score (sum of 6 of 8 items) and the 8 items separately
- Control of Eating Questionnaire (CoEQ): Scores from the 4 domains and scores from 19 individual items

The PRO questionnaires, SF-36v2™, DTSQ and CoEQ will be used to evaluate the objective regarding Quality of Life. Each of the PRO endpoints will be analysed separately as the other continuous efficacy endpoints for the primary estimand using a similar model approach as for the primary endpoint with the associated baseline and post-baseline responses as covariates.

## 3 Changes to the statistical analyses planned in the protocol

The changes to the statistical analyses planned in the protocol are described in the table below.

Change to planned statistical analysis	Rationale for change
Italy removed from pre-defined region Europe to be used in the statistical analysis (Section <a href="#">2.1</a> ).	Italy was not included in the study.
References updated in Section <a href="#">2.2</a> and <a href="#">2.4.2</a> .	Updated for correctness.
The word nominal removed from the sentence “The closed testing procedure described in Bretz et.al. 2011 combined with a hierarchical approach is used to control the overall type-1 error at a nominal two-sided 5% level. “	Updated for clarification and to clearly distinguish the level used for testing and the level at which the overall type I-error is controlled.
Definition of DXA analysis set added (Section <a href="#">2.3</a> )	Was not specified in the protocol.



Specification of the PP-analysis set criterion on including 'subjects on trial product at week 28 and having at least one non-missing HbA <sub>1c</sub> measurement at or after week 28'. This was revised to 'subjects on trial product at <u>visit 8</u> and having at least one non-missing HbA <sub>1c</sub> measurement at or after <u>visit 8</u> (Section <u>2.3</u> ) .	Revision was done to ease programming. Visit 8 corresponded to week 28 ±7 days.
Wording on the multiple imputation model for the primary analysis updated to specify that observed <u>or imputed</u> values will be used as covariates (Section <u>2.4.1</u> )	Updated for clarification.
The 'in-trial treatment policy' sensitivity analysis is renamed to 'retrieved drop-out' analysis and it is clarified that the model will only be conducted to test the robustness of the superiority hypotheses (Section <u>2.4.5.2</u> ).	Per new preferred terminology, this type of analysis is no longer called an 'in-trial' analysis, but rather a retrieved drop-out analysis.
It was specified that the tipping point analyses for the confirmatory secondary endpoints are carried out on FAS and the DXA analysis set respectively.	Updated for clarification.
<p>The following clarifications for the analyses of the confirmatory secondary endpoint, total fat mass (kg), in the DXA sub-study was added (Section <u>2.5.1</u>):</p> <ul style="list-style-type: none"> <li>For all analyses it is clarified that the analyses are based on the DXA analysis set and that stratification factor will not be included in the models.</li> <li>Clarification that no MCMC-imputation will be performed</li> <li>For the in-trial sensitivity analysis, imputation will be done within the same group of randomised treatment irrespective of status of treatment completion and region will be included in the imputation model. The analysis was re-categorised to a supplementary analysis.</li> <li>Clarification of the in-trial period for DXA assessments</li> </ul>	<ul style="list-style-type: none"> <li>The DXA analysis set is the relevant population and stratum DXA/non-DXA is redundant in the analysis of DXA endpoints.</li> <li>With only 1 post-baseline measurement, non-monotone missingness is not possible and MCMC-imputation is redundant.</li> <li>No systematic collection of off-treatment DXA scans are done according to protocol (only premature treatment discontinuers not completing the premature end of treatment DXA scans are planned to have an off-treatment scan at the last visit). The data therefore does not support imputation by status of treatment completion. The coarser imputation approach is not expected to lead to sparse data issues, so there is no reason not to include region in the imputation model.</li> <li>Re-scans for DXA can occur after the P11 follow-up visit.</li> </ul>

It was clarified for statistical analyses of the supportive secondary body composition endpoints in the DXA sub-study that the analyses were to follow the same approach as for the confirmatory secondary endpoint, total fat mass (kg), (Section <a href="#">2.5.2.1</a> ):	Data is collected in the same way and similar analysis considerations as for total fat mass (kg) apply.
Wording updated for the description of multiple imputation for binary endpoints (Section <a href="#">2.5.2.1</a> )	Updated to clarify that no new imputations are done.
Wording updated on analyses of amylase and lipase (Section <a href="#">2.5.2.2</a> )	Updated to clarify that baseline values of amylase and lipase should be log-transformed before being used as covariates in the analyses.
Wording updated on analysis on pulse rate (Section <a href="#">2.5.2.2</a> )	Updated to clarify that pulse rate should not be log-transformed.
For HbA <sub>1c</sub> , total fat mass, total lean mass and visceral fat mass the unit is corrected to '%-point'(multiple places).	Updated for correctness.
Number of imputations revised from 200 to 500 (multiple places).	Revised to align with the other NN9535 phase 3b trials.

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